PHYSIOLOGY

Current Trends and Future Challenges

Companion Essays

Physiology - Current Trends and Future Challenges

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The Progress of Physiological Sciences

Debabrata Ghosh, Jayasree Sengupta*[1,2]

Department of Physiology, All India Institute of Medical Sciences, New Delhi, 110029, India. [1]Presently retired

*Chair of the Board of General Assembly, International Union of Physiological Sciences (IUPS)

Email addresses:

DG: debabrata.ghosh1@gmail.com

JS: jsen47@gmail.com

Running Head: Progress of physiological sciences

[2]Corresponding author

Abstract

In the present paper, an attempt has been made to briefly describe how physiological sciences as a as a broad scientific discipline and a mother science with core and non-core sub-disciplines traversed through the path of integrative discourse since the European Renaissance till today's ventures at new higher levels of integration from 'gene to tissue to organism.'

Key words:

Integrative physiology, Logic of life, Quantitative biology

Introduction

Physiology is a branch of biology which studies all properties and functions of the living body, including mechanical, physical and biochemical. Physiology also intends to study how living body responds to external and internal stimuli, including exercise and stress, environmental conditions and disease in an integrated manner. Thus, physiology is essentially an integrative discourse towards understanding the life process in a given environment. The aim of this essay is to examine how physiological sciences progressed in time to the present state of Integrative Physiology taking up an interesting challenge of undertaking its movement from 'gene to tissue to organism.'

D'Arcy Thompson in the Introductory section of his *On Growth and Form* (37) writes:

> 'Of the chemistry of his day and generation, Kant declared that it was a science, but not Science - *eine Wissenschaft, aber nicht Wissenschaft* - for that the criterion of true science lay in its relation to mathematics...We need not wait for the full realisation of Kant's desire, to apply the natural sciences the principle which he laid down. Though chemistry fall short of its ultimate goal in mathematical mechanics, nevertheless physiology is vastly strengthened and enlarged by making use of the chemistry, and of the physics, of age. Little by little it draws nearer to our conception of a true science with each branch of physical science which it brings into relation with itself: with every physical law and mathematical theorem which it learns to take into its employ. Between the physiology of Haller, fine as it was, and that of Leibig, Helmholtz, Ludwig, Claude Bernard, there was all the difference in the world.'

Elsewhere he comments, '...the physiologists has long been eager, to invoke the aid of physical or mathematical sciences; and the reasons for this... lie deep, and are partly rooted in old tradition and partly in the diverse minds, and temperaments of men' (37). What 'old tradition' and which 'diverse minds' D'Arcy Thompson might have indicated in 1917, the year of the first publication of *On Growth and Form*? In the following sections, we shall discuss about the major coordinates in the journey of physiological sciences and physiologists, that gives shape to the present state of physiological sciences.

Kantian world view and Hegelian dialectics to analyse the history of progress

The idea that integrated gathering of knowledge and beliefs about material truth proceeds through the dialectics of 'abstraction - interrogation - investigation - concretisation' might have been perceived quite early by the human mind as indicated in many tales of ancient scripts from China and India. However, most historians believe that this was best expressed in form of the triad of 'thesis – antithesis – synthesis' in the deliberations by Immanuel Kant (1724-1804) and then it was expounded first by Johann Gottlieb Fichte (1762-1814) and later by Georg Wilhelm Friedrich Hegel (1770-1831). Hegelian dialectic movement from thesis to antithesis to synthesis is guided by three basic principles. First, anything and everything material is made out of opposing forces or sides, meaning there is always some element of contradiction – within or without or both – in a developing body. Second, quantitative changes lead to qualitative change, meaning gradual changes lead to leaps or jumps or turning points which may result in transformation. Thirdly, there is negation of the negation resulting in spiralling, not circular, movements in process. Thus, according to Hegelian dialectics, a thesis, because of the reaction from its action and process of development, falls into the negative of itself, and in the course gives rise to antithesis which contradicts or

negates or challenges the thesis, and it is resolved by means of a synthesis (32). Thomas Kuhn, in his *The Structure of Scientific Revolutions*, has explained how such progressive process is associated with 'paradigm shift' in science (23). In fact, physiological sciences has experienced such paradigm shifts in its course of development over time by integrating first physics and chemistry, and then mathematics and systems analysis. In recent times, convergence of trajectories from ecological and evolutionary physiology, and more recently from molecular biology has resulted a new synthesis in approaching Integrative Physiology. In the following sections, brief stories of the major mile-stones in this journey path shall be discussed.

Jean Fernel - the first mover of comprehensive physiology

Jean François Fernel (1497?-1558) is probably the first Renaissance physiologist who attempted for the first time to effectively demonstrate how the elemental attributes of the body parts are woven into a whole that manifests all the temperaments, humours, powers and faculties of living organisms based on principles of deductive reasoning, causal analysis and physics (40). Fernel studied mathematics, philosophy, astronomy, anatomy and function of the human body with huge alacrity and made a serious attempt to give birth to the concept of comprehensive physiology in the womb of Hippocratic – Aristotelian – Galenic thesis and pushed hard to integrate the discourse of physiology with physical objective analysis, and to think physiology in integrative manner. Thus, he was the first to use the term 'physiology' in its modern scientific sense in 1542 which was the year of first publication of *Physiologia*, when 'physiologia' used to denote the study of nature or natural philosophy. Fernel was critical about illustrated anatomy based texts at the centre stage of contemporary medicine as he considered this shallow and lacked integrative principles of causation of bodily functions.

In his *Physiologia*, he reflected upon analytical approach, and settled on a 'top-down' method, which is recognized in today's physiological practice as well. He then described all the known anatomical parts and developed his idea of 'comprehensive physiology' of the human organism (33). Fernel's comment about five hundred years ago, 'Anatomy is to physiology as geography is to history; it describes the theatre of events' creates an awe in the mind even today (38).

Claude Bernard - the prime mover of modern Integrative Physiology

In the next century, Galileo Galilei (1564-1642) and his scientific methods using tools, observations and mathematics in one hand, and René Descartes (1596-1650) and his rationalism and anti-authority teachings on the other hand, played major role in the induction of scientific revolution of the 17th century which paved the path for new experimental integrative physiology best embodied in William Harvey (1578–1657) as discussed elsewhere (1). It took another one hundred and fifty years after Harvey, physiology being approached during this period in integrated manner involving quantitative mechanics, physics, chemistry and mathematics by Albrecht von Haller (1708-1777), Hermann von Helmholtz (1821-1894), and Carl Ludwig (1816-1895) towards the arrival of Claude Bernard (1813–1878) in the 19th century (17).

Claude Bernard propounded the concept that body systems function such manners as they do to maintain a constant internal environment, that is *milieu intérieur*. He emphasized that an organism is able to adjust itself to external physical and chemical variations by maintaining permanence of its *milieu intérieur* because of integrative control systems involving the cells,

the organs and the organisms. Like Jean Fernel, Bernard was always attentive not to explain all his observations only by anatomy, since according to him, anatomy was to serve explanation of physiological complexity. Physiologists must start from studies of physiological phenomena to explain them in the whole organism and not try to explain a function from an organ (6).

In many ways, Bernard through his robust practice and theory paved the path of modern Integrative Physiology with emphasis on the physicochemical basis of various physiological phenomena. In this process, Bernard steadfastly fought against three basic antagonistic forces: (i) popular theory of vitalism, that is the whole living cell or organism is more than simple sum of its parts, and this holism of life is explained by action of a vital force which neutralizes the negative effects of physico-chemical forces in living organism, (ii) teleology (or teleonomy) based on attributions of 'providential destiny' on life processes making physiological processes mystic, and (iii) philosophy of pan-optimism. Thus, Claude Bernard had to fight against any philosophy and notion that had resulted in mystification of life. He believed that Science should always explain obscurity and complexity by clearer and simpler ideas and there is no place of vitalistic explanation in physiology (6). He insisted that physiologists must therefore seek the true foundation of animal physics and chemistry in the physical-chemical properties of the inner environment of the organisms. The life of an organism is simply the result of all its innermost workings (6).

Walter Cannon and Hans Seyle - Further movement of Integrative Physiology to form the basis of modern medicine

Bernardian notion of integrated physiology was closely followed by another great physiologist, Walter Bradford Cannon (1871–1945) in the 20th century. Bernard's theory addressed 'whys' of bodily processes by postulating that they help maintain a constant internal environment. Based on a series of magnificent experiments over almost three decades, Walter Cannon in fact examined the 'hows'. Cannon established the concept of 'homeostasis' in the theory of physiology, by which he referred to the stability of the inner sphere of the body. Both Bernard and Cannon postulated the actions of control systems operative at different levels and made the foundation of today's Integrative Physiology. Subsequently, physiological sciences expanded largely on Bernard-Cannon's kinetic model of negative feedback that explained regulation of monitored variables of the body at steady-state levels (16). In continuity of Cannon's model of 'Fight-or-Fright', Hans Selye (1907-1982) postulated around 1930s the modern concept of stress as a novel integrative physiological basis of medicine. According to Seyle's model, 'stress' reflects the difference between afferent information about conditions as sensed and the homeostatic set point for responding, and it may be conceptualized in terms of the error signal in a homeostatic negative feedback loop, with the integrated error signal as a measure of accumulated stress over time, resulting in what Seyle termed as 'heterostasis' (16,34). It is generally viewed that the efforts of Hans Seyle in the continuity of Walter Cannon's endeavour of theorizing physiological regulations was a serious historic attempt towards integrative scientific medicine involving multiple systems affecting the whole organism (16,34).

Emergence of ecological and evolutionary physiology

Around the same time, another tributary of physiological sciences began an interesting journey by blending of the traditions of comparative physiology and natural history. August Krogh's postulation, 'For a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied' triggered a strong desire among the physiologists to undertake cross-disciplinary integration between animal physiology and the field of natural history (22). The former was progressing in physiological laboratories during the latter half of the 19th century and early 20th century. It has meanwhile developed a large and impressive body of data through rigorous protocol of experimental design and analysis on various physiological processes in different kinds of animals. The field of natural history, on the other hand, was already well-developed in the 19th century, and contributed a substantial knowledge base of animals, sometimes very unusual animals, and their habits under natural conditions in the field. The merger of these two areas resulted in experimental scientists undertaking research on non-traditional animals and referring the results of that research to the behaviour and functional responses of species under natural conditions. Animal ecological physiology began to assume a prominent place in modern Integrative Physiology since 1940's with the seminal contributions of George Bartholomew (1919-2006), Knut Schmidt-Nielsen (1915-2007) and many other investigators. Ecological physiology is concerned with the function and performance of organisms in their environment with a major objective to understand the underlying physiological, morphological, biochemical and molecular attributes of organisms with respect to the constraints imposed by the environment (5,12).

C.L. Prosser in his 1950 book on *Comparative Animal Physiology* delineated five broad objectives of ecological physiology (30):

> '(1) to describe the diverse ways which different kinds of animals meet their functional requirements; (2) to elucidate evolutionary relationships of animals by comparing physiological and biochemical characteristics; (3) to provide the physiological basis of ecology . . . ; (4) to call attention to animal preparations particularly suitable for demonstrating specific functions; and (5) to lead to broad biological generalizations arising from the use of kind of animal as one experimental variable.'

Garland and Carter (15) suggested that these broad objectives subsequently led to the notion of modern evolutionary physiology. Yet, attributing that thinking of evolution in physiology and vice versa only emerged with evolutionary physiology is factually not correct. A strong group of Russian physiologists, for example I. M. Sechenov (1829-1905), I.P. Pavlov (1849-1936), and N. E. Vvedenskii (1852-1922) reportedly contributed to this field long since. The term “evolutionary physiology” was probably coined by A. N. Severtsov in 1914, and the person most responsible for the creation of Russian evolutionary physiology was Leon Orbeli (1882-1958). In 1920s, Leon Orbeli devised the scientific method for studying evolutionary physiology, defined the main objectives, and outlined the direction in which it should develop. Many classical studies of comparative and environmental physiology interpreted patterns as the outcome of adaptive evolution. Moreover, physiologists have long exploited the results of evolution in choosing the most appropriate species for investigation of physiological problems, as well as, evolutionary analysis of the physiological impact of specific gene alleles. Evolutionary biologists such as Sewall Wright (1889-1988), Richard Goldschmidt (1878-1958), and Theodosius Dobzhansky (1900-1975) had major research foci

on 'physiological genetics'. Physiology and Evolutionary Biology, nonetheless, remained separated from one another until 1970s (14).

Several seminal developments during 1960 to 1980 elicited a substantially increased constructive merger of evolutionary biology into the physiological sciences. In November 1961, Ernst Mayr in his paper “Cause and effect in biology" distinguished the notion of proximate causes from that of ultimate causes in biological effects (25). A proximate cause is an immediate, mechanical influence behind a trait, explaining how a trait in an organism is displayed. Ultimate causes are historically rooted explaining why an organism has one trait rather than another, often in terms of natural selection. Although the proximate-ultimate distinction had been mentioned as early as in 1938 by J. Baker (2), the provocative paper of Ernst Mayr (25) triggered an intent among a subset of functional physiologists and ecological physiologists to have a new look to the physiological explanation of function in the light of evolution. The expression 'in the light of evolution' although used by Julian Huxley in the 1950s (19), was later popularized by Theodosius Dobzhansky in his proverbial statement, "Nothing in biology makes sense except in the light of evolution" in his 1973 article bearing the same title (11).

One very significant step in the emergence of the field came from a workshop sponsored by the U.S. National Science Foundation, held in Washington, DC, in 1986, which resulted in an edited volume with the title, *New Directions in Ecological Physiology* (13). Pough then used the term "evolutionary physiology” to entitle a review in 1988 (29). Later, Diamond (10) and then Garland and Carter (15) codified the term - Evolutionary Physiology - to designate the

emerging area of the integrative physiological sciences. In 1994, the U.S. National Science Foundation established a formal *Program in Ecological and Evolutionary Physiology*. There has been an impressive growth in this area of integrating physiological sciences since that time (14).

Present day status of physiology sciences

In a nutshell, the expansion of physiological sciences in the first half of the 20th century took place in the line of Bernard-Cannon's approaches to integrative physiology based on physicochemical explanations and integrative modelling. August Krogh (22) had penned down the soul of this progress of physiological sciences succinctly in his paper, "The Progress of Physiology." Subsequently, in the second half of the 20th century the physiological sciences witnessed significant integrative confluences with ecology and evolutionary biology generating a promise of 'developing a quantitative understanding of biological design' (10). Further, two parallel lines of development, namely (i) physicochemical theories of self-organisation that arose from Lotka's theoretical and Bray-Belousov's experimental work on chemical oscillations and then Belousov-Zhabotinski's model of chemical oscillator on one side, and (ii) biological theories of self-organisation evolved in the womb of artificial intelligence and cybernetics on the other side, culminated in the 1970s giving rise to a paradigmatic development (31). The target of quantitative understanding of biological design and its pattern analysis became even more palpable by the emergence of application of systems analysis to biological and physiological problems. The credit of applicability of systems analysis to biological and physiological problems is generally attributed to Norbert Wiener (1894-1964).

Wiener writes in his *Cybernatics, or Control and Communication in the Animal and the Machine* published in 1948 (41):

> '...the present time is the age of communication and control...whether in the metal or in the flesh...and its cardinal notions are those of message, amount of disturbance or "noise" - a term taken over from the telephone engineer - quantity of information, coding technique, and so on.'

Wiener's biocybernetics plays a dominant role in today's theoretical biology by integrating different levels of information to explain how biological systems function. Wiener's theory of feedback regulation and its application for explanation of the mechanisms of homeostasis is considered as singularly most important contribution of cybernetics to integrative physiology and medicine and taken as a benchmark of the beginning of post-modern phase of physiological sciences (42). The entire scenario is well testified by John Brobeck when he writes in *Physiological Controls and Regulations* published in 1965 on the hundredth anniversary of Claude Barnard's *L'Introduction à l'étude de la Médecine Expérimentale* published in 1865 (9):

> 'One can now say that physiology has its foundations in three – not just two – fundamental sciences. The first is physics and the second is chemistry, both of which began to be applied to biological problems in the nineteenth century. The third is systems analysis based upon communications theory; its usefulness is only just beginning to be appreciated.'

The advent of molecular biology techniques and effective applications of control and communication engineering to molecular bioinformatics during the decades following 1980s,

promptly resulted in a preoccupation with the problems and challenges inherent in these techniques, sometimes at the expense of the original perspectives and concepts. Many new mechanisms that have been discovered at the molecular level, as well as, their economical exploitation have contributed to a climate of reductionism. Among the scientific community, it created a dominating bias for molecular biology and a perception that the discipline of Physiology is in crisis (3,8,17). The root of such perception stemmed from the confusion between the biological questions to be solved and the methods/technologies to be applied. The study of control mechanisms, in fact, can be applied on functions at any level - subcellular, cellular, and organ, and reaches its highest level of complexity with the functioning of the body as a whole and its interaction with the external environment. This involves the determination of the interaction between genetic and environmental factors and the resulting integrated body adaptation. In the pursuit of these questions, it is apparent that any appropriate combination of techniques are to be used for examining biological information at any organizational level. Despite the undeniable and spectacular successes of molecular biology, the need for an integrative perspective has become increasingly evident. This is particularly true in many clinical cases of gene and drug therapies that failed despite promising results from defined animal models (39). In such a dominion of hiatus in understanding of physiology which would attempt to place the descriptive facts and proximate mechanisms of molecular and cellular biology into quantitative context, Integrative Physiology as a discipline comes with promises of providing significant inputs (28,39).

On the occasion of the 1993 Congress of the International Union of Physiological Sciences (IUPS) held in Glasgow, Charles Boyd and Denis Noble edited an anthology bearing a

provocative title, *The Logic of Life - The Challenge of Integrative Physiology*. The Preface of the book starts with a reference to a statement given by Sir James Black, a 1988 Nobel laureate pharmacologist, about his views on the future of the health of science that it would be 'the progressive triumph of physiology over molecular biology' (26). Sir Black (7) writes in the Foreword Section of the same book:

> 'The repertoire of chemical messengers is already extensive - mind-boggling in fact - because we currently have no conceptual framework to integrate them. So the biochemical properties and components for physiological control by convergent amplification are known to exist. The point here is that trying to modify such systems pharmacologically will present us with great problems. Hopes of realizing the optimistic forecasts about the benefits that molecular biology will bring to pharmacology are likely, I believe, to be circumscribed by the state of physiological knowledge, models, and concepts.'

Meanwhile, with the completion of the Human Genome Project and with the advent of the '-omics' technologies, systems biology emerged with an aim to move beyond the traditional reductionist molecular approach towards a more holistic approach by studying networks and interactions between individual components of networks. However, to date systems biology has been applied to relatively simple systems, and has not been applied to studies of controls and communications in complex organisms, a field that has traditionally been the domain of physiological sciences. Clearly, physiology and systems biology share the goal of understanding the integrated function of complex systems from the level of genes to the whole organism. It appears imperative that physiologists embrace the cornerstones of researches in functional genomics, genetics, different animal model organisms, computational

biology, and interdisciplinary research efforts and they must move away from naive reductionism and reemphasize the central importance of integration and synthesis in their research and teaching of physiological sciences. These issues have recently been discussed in several articles (18,21,24,35).

In today's physiological sciences, all of the sciences that include anatomy, biology, biochemistry, biomechanics, chemistry, mathematics, physics, physiology and statistics converge contributing to measure the response of biological systems. This issue has been succinctly summarized in a recent document titled, *Health of Physiology* (36) published by The Physiological Society, U.K. (Figure 1). Thus, present day physiology is multi-disciplinary in approach towards deciphering physiological processes differentiating at multiple levels throughout wide range of scales and their integration (4,18,21,24,35).This requires knowledge of interrelationship among macromolecules, cells, tissues, organs and systems in the body, and also the position and ability to utilize advanced technologies in numerical data development and their analysis. Physiology today - according to the IUPS - intends to encompass the study of the functions and integrative processes of life at all levels of structural complexity between the molecular level and that of the whole organism. It includes all organisms, and frames function in evolutionary, environmental, ecological and behavioural contexts. It embraces a cross-disciplinary approach to modern science, through which physiologists aim to achieve translation of this knowledge into the health of humans, animals and ecosystems (20). This constitutes the major mission of IUPS to be fulfilled with the help of eighty associated bodies all over the world (27).

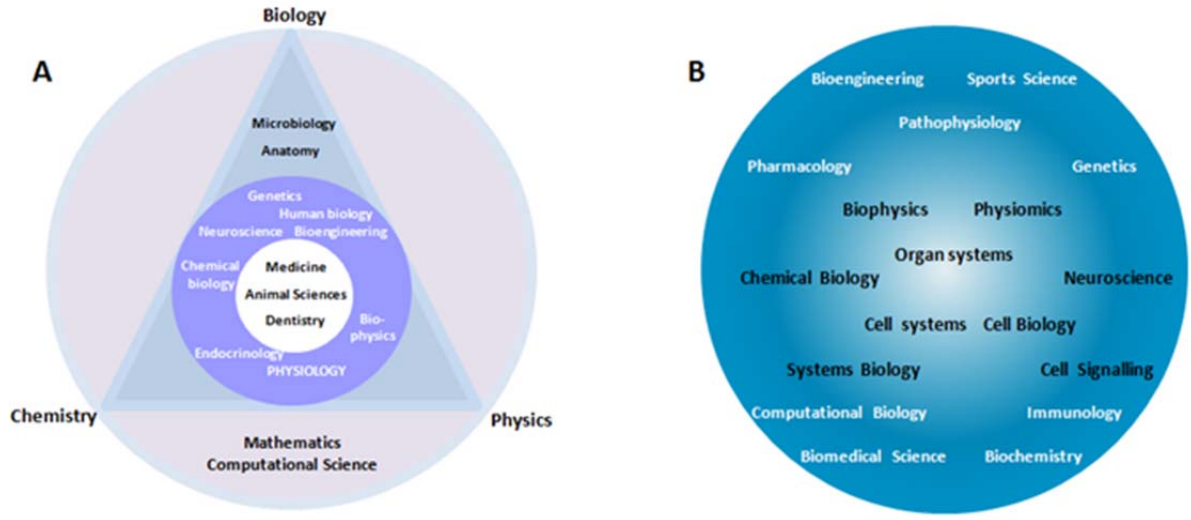

Figure 1. Defining physiology. Physiology as a broad scientific discipline spans from the molecular and cellular level to the organ, tissue and whole system levels, and provides a bridge between the basic sciences and the applied medical sciences (A). Physiology is a mother science with core and non-core sub-disciplines. Areas such as cell systems and systems physiology form the core of the discipline, while bioengineering and sports science are examples of related disciplines overlapping with physiology at its perimeter (B). Based on Health of Physiology (36).

Conclusion

Historically, physiological sciences traversed the path of integrative discourse since the European Renaissance with a mission to understand the life process in a given environment. With Bernard-Cannon's experimental legacy along with increasing knowledge in the domain of ecological and evolutionary physiology on one side, and newer genomic, cellular, molecular and computational tools on the other side, today's Physiology - as it appears now - can venture at new higher levels of integration and that a genuine, quantitative theory of biology may eventually be developed though future research in Integrative Physiology. Today's Physiologists cherish to realize their innate longing that physiology is to understand the logic of life.

Acknowledgement

DG acknowledges the grant of Learning Resources by the All India Institute of Medical Sciences - Delhi.

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Physiology of the Musculoskeletal System and its Control: Topics of Current Interest and Trends in Publication

Janet L. Taylor*

Neuroscience Research Australia, Sydney, Australia

School of Medical Sciences, The University of New South Wales, Sydney, Australia

School of Medical and Health Sciences, Edith Cowan University, Perth, Australia

*Chair of the International Union of Physiological Sciences, Commission I-Locomotion

Address for correspondence:

Dr. J.L. Taylor

Neuroscience Research Australia

Barker St, Randwick,

NSW, 2031.

Email: j.taylor@neura.edu.au

Running Head: Publication trends in the physiology of movement

Abstract

In the terminology of the International Union of Physiological Sciences (IUPS), 'locomotion' is a shorthand for the physiology of the musculoskeletal system and its control. The tissues and systems included are the skeleton, the skeletal muscles and tendons, and the components of the nervous system that organize and control movements of parts of the body or the whole body. This essay on the current state of research into the physiology of 'locomotion' has two sections. First, there is a brief overview of topics that are of current interest in the area. These topics were identified through search of highly cited publications over the past 5 years. Second, some trends in publication of original research articles about the tissues and systems that subserve movement are reported. Overall, the rate of publication on these research subjects has increased by more than half over the last ten years. As the number of these publications designated as 'physiology' has stayed constant, the proportional contribution of 'physiology' has decreased. While there are exciting recent findings on the physiology of the musculoskeletal system and its control, and challenges in understanding remain, physiology research in these areas is holding steady rather than growing.

Keywords:

Locomotion, Physiology, Muscle, Bone, Motor System

Introduction

While locomotion, defined as 'movement from one place to another', may seem a relatively circumscribed area of physiology, the IUPS Commission title, Locomotion, can be thought of as shorthand for the musculoskeletal system and its control. Hence, the tissues and systems that should be considered include the skeleton (bones, cartilage and ligaments), the skeletal muscles and tendons, the neural elements that directly link to the muscles (motoneurons and muscle afferents), the spinal networks that subserve rhythmic movements plus all components of the nervous system that organize and control movements of parts of the body or the whole body. The parts of the nervous system that contribute to movement control include, but are not limited to, the motor areas of the cortex, basal ganglia, thalamus, brainstem, cerebellum and spinal cord. Moreover, most of the sensory systems, including proprioception, vestibular sensation, touch, pain, vision, and hearing link to motor output through various dedicated pathways, which do not require the sensory signals to reach conscious perception.

This essay will briefly consider the current topics of interest to researchers within the area of the musculoskeletal system and its control. This overview has been compiled based on highly cited articles that were published in the last 5 years. The essay will then examine the trajectory of publications that address the musculoskeletal system and its control and are designated to be in the research area of physiology.

Current topics of interest

The physiology of the musculoskeletal system and its control can be divided into several notional areas: 1) the peripheral substrate of the system and its maintenance, i.e. bone homeostasis and remodeling, and muscle mass maintenance, atrophy and hypertrophy; 2)

musculoskeletal tissues as endocrine organs, i.e. secretion of factors that influence more distant organs; 3) the effects of exercise in health and disease; 4) the contractile function of muscle; 5) the control of muscle by the nervous system, i.e. spinal and brainstem networks, cerebellum, basal ganglia, cortical areas and the interactions between them; 6) activity-dependent plasticity of the nervous system related to the control of muscles, i.e. changes in the nervous system with motor learning or training. Examination of highly cited papers published over the past five years points out some areas that have been of particular interest (Fig. 1).

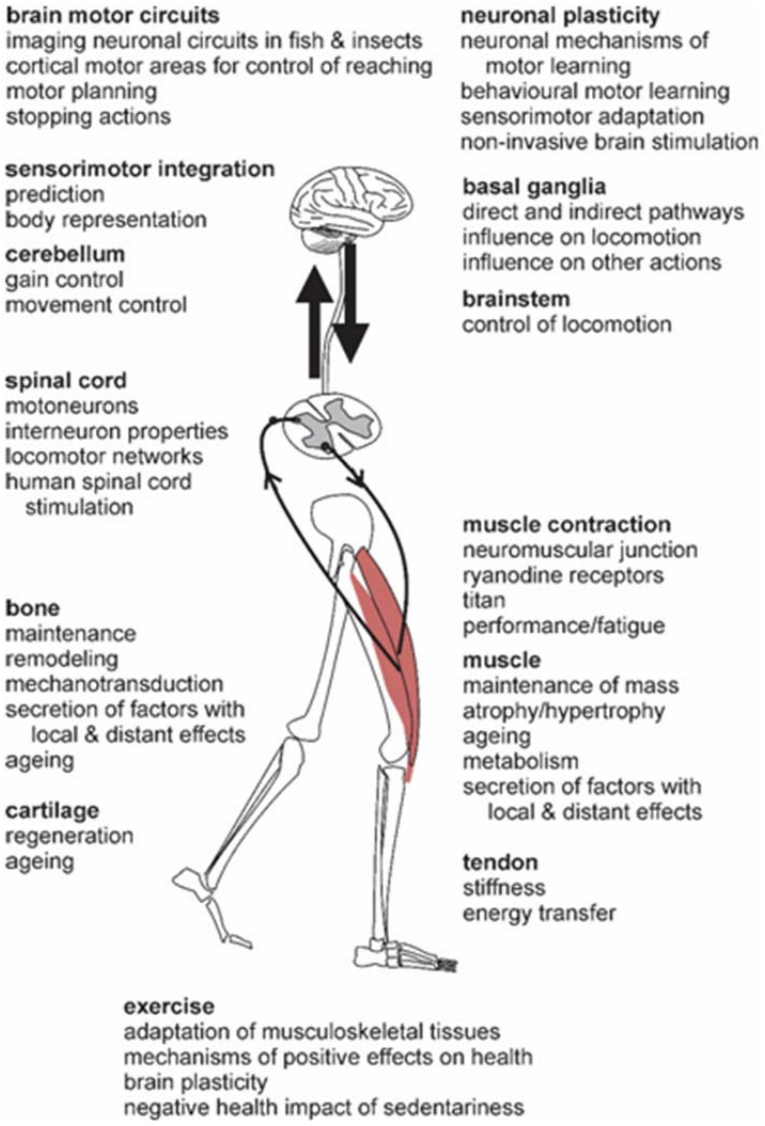

Figure 1. Current topics of interest in the musculoskeletal system and its control.

For bone, the osteocyte has come to the fore with interest in its mechanism for response to mechanical perturbations, the factors it releases and their local and more distant effects (8,15,27,47). These areas link to understanding bone homeostasis and remodeling with local signals from bone cells, interactions with muscle, and hormonal influences from more distant organs. Moreover, the influence of factors released from bone (e.g. FGF23 and osteocalcin, sclerostin) on skeletal muscle and cartilage, and other organs including the kidney and heart has begun to be recognised (15,49).

For muscle, the maintenance of muscle mass, atrophy with disuse and hypertrophy with exercise have proved of interest at levels from intra and extracellular signaling pathways through to the influence of specific nutrition and exercise regimens on protein metabolism and performance (4,9,12,22,39). Ageing muscle and why it becomes impaired has also drawn attention (31, 45). The possibility of reversing this decline by exposure to a young environment is particularly intriguing (13, 43). Similar to bone, the factors released by muscle and their effects on distant tissues are becoming better understood, including interactions with adipose tissue (34). However, there is controversy over the measurement of some secreted substances (e.g. irisin; 3, 25).

Exercise with its mechanical and metabolic effects on muscle and bone is paramount for the maintenance of both tissues (18, 22, 49). Moreover, the endocrine roles of the tissues, i.e. their secretion of osteokines and myokines, and the participation of muscle in glucose metabolism depend on exercise (33, 34). Hence, how exercise maintains health and ameliorates disease is of major interest at levels from the signaling of released factors and their specific actions through to what specific exercise is best for human health (e.g. 22, 35).

Of particular current interest is how much or what kind of exercise can counter the negative health impacts of prolonged sitting (5, 16).

While aspects of muscle contraction are well understood, new imaging techniques have allowed the ryanodine receptor, and hence its molecular mechanisms and interactions, to be described in more detail (e.g. 17, 48). A new role for titin has also been proposed and this may start to fill some of the holes in our understanding of the mechanisms of eccentric (lengthening) muscle contraction (41).

There have been new findings and advances in understanding of the control of movement at all levels of the nervous system. The use of rabies virus to trace pathways antidromically, gene manipulation, optogenetic activation of specific cell types and calcium imaging in vivo has given unprecedented opportunities to identify motor networks and examine the contributions of different cells. In the spinal cord, the networks that underlie rhythm generation are being identified (e.g. 26). Amongst other findings, for which the functional consequences are not yet clear, is the identification of gap junctions in mixed synapses associated with afferent input to the motoneurons in adult rats , while in zebrafish, locomotor rhythm is influenced by retrograde control of some premotoneurons via gap junctions from motoneurons (7,44).

One example of the use of optogenetics comes from the demonstration of the effects of specific cell types in the mesencephalic locomotor region (MLR) in the brainstem on locomotion; glutamatergic neurons start and drive locomotion, cholinergic neurons modulate locomotion and GABAergic neurons stop it. The optogenetic investigation was combined with electrophysiology to tease out the influence of the basal ganglia on the MLR neurones

(38). More widely, the way in which the direct and indirect basal ganglia pathways control movements other than locomotion is a topic of current interest, as is the role of the cerebellum in movement control and the interaction of the cerebellum and basal ganglia (10,11,14,21). Similar techniques can be used in cortical areas to perturb specific areas to identify their contribution to motor planning and movement (28), or to investigate how motor activity alters responses to sensory stimuli (20,29).

The capacity for integration of knowledge from neurons through to behavior is increasing. It is now possible to examine the integrated working of motor circuits of the whole brain of larval zebrafish through optical calcium imaging of neural activity (2). Similar techniques are being extended to mice and non-human primates where optical imaging will not allow a view of the whole brain but will allow the activity of populations of neurons to be measured simultaneously (32). Optical imaging has also allowed longitudinal studies that were not possible with electrophysiological recordings. Imaging of specific neurons over weeks has given new insights into the changes of dendritic structure and neuronal activity that occur during the process of motor learning (19, 24).

Motor learning in humans is also a topic of strong interest, with functional magnetic resonance imaging used to identify changes in functional connectivity between brain circuits over time. In particular, integration between visual and motor areas decreased, and other areas disengaged, as a visually-guided learned motor sequence became more automatic (6). Other areas of recent interest range from how movements are stopped to how prediction of sensations produced by movements allows better perception and better performance. Functional imaging, tractography, EEG analysis and cortical recording have all been employed to examine the interactions between inferior frontal gyrus, pre-supplementary

motor area and subcortical nuclei to delineate inhibitory circuits (36, 46). However, measures of performance also continue to provide insight into physiological processes (e.g. planned movements can be stopped up to ~200 ms prior to the movement initiation; 40).

The goal of understanding the selection, production and adaptation of motor behaviours is coming closer, but the challenge remains to link insights at a neuronal level to changes at the level of human performance. For human physiology, measurement of brain activity is limited to non-invasive techniques and restricted recordings in patient populations. Therefore, neuronal models are needed to make predictions that can then be tested through non-invasive recording or stimulation techniques, or through performance of perceptual or motor tasks (42). Currently, modeling of human cortical activity is making progress with the practical aim to translate brain activity into machine commands that can control robotic prostheses or bypass the spinal cord to produce muscle contraction through electrical stimulation (1, 23).

Overall, there are interesting new findings on the homeostasis of the musculoskeletal system, its links to the endocrine system and the role of exercise in health and disease. Progress is also being made in understanding the neural and muscular mechanisms underpinning the primary function of the musculoskeletal system, i.e. to move the body or parts of the body.

Publications related to the musculoskeletal system and its control over the past 3 decades

One way to describe the state of physiological research into the musculoskeletal system and its control is through the number of research articles published in the area. Table 1 shows publication numbers from searches through the Web of Science performed with simple search terms relevant to musculoskeletal control and confined to research articles. While the search

terms will by no means capture all publications in the area, they should give a reasonable sample. Publication numbers listed for 'all terms' were derived through a combined search and count each publication once. As search terms were not mutually exclusive, publications may be represented under more than one topic. Of ~1.26 million articles published since 1900 and relevant to the selected topics, ~63 thousand (5%) are identified to be in the research area of physiology. These 63 thousand 'locomotion' physiology papers make up ~14.5% of the total 430 thousand papers with the subject area physiology.

Table 1: Total number of publications indexed in Web of Science for the listed 'locomotion' topics and those identified by the research area 'physiology'

	Total Pubs (thousands)	Physiology Total Pubs (thousands)	Physiology (% total)
bone	527.4	6.0	1.1%
cartilage	67.8	0.8	1.2%
ligament	53.5	0.7	1.3%
skeletal muscle	142.0	24.2	17.0%
tendon	45.4	1.4	3.2%
motor unit	4.7	1.3	27.1%
motoneuron	28.6	3.6	12.7%
motor nervous system	18.0	1.2	6.9%
locomotion	33.7	2.5	7.4%
walking/gait	129.3	3.3	2.6%
voluntary movement	8.8	1.2	13.6%
exercise	250.4	28.1	11.2%
motor control	94.6	5.2	5.5%
all terms	***1262***	***63.1***	***5.0%***

The total number of publications for each topic can be compared with those identified as physiology. Table 1 emphasizes that a large proportion of physiology publications in 'locomotion' address the topics of bone, skeletal muscle and/or exercise. Also of note is that the 6000 publications on bone in the area of physiology account for a small proportion of the total publications on this topic. That is, papers on bone contribute >9% of the physiology

papers but physiology contributes only 1.1% of the bone papers. By contrast, physiology contributes ~17% of skeletal muscle papers and ~11% of exercise papers.

Trajectory of publication over the past three decades

Overall, the numbers of 'locomotion' publications identified as physiology have risen across the past three decades. Of the 63 thousand publications, some 25 thousand have been published in the last ten years (2007-2016) compared with 19.5 thousand in the previous decade (1997-2006) and ~19 thousand prior to 1997. Table 2 breaks down the total by topic and shows that 28-49% of all papers in each 'locomotion' topic were published in the most recent decade. Papers on exercise (48%), skeletal muscle (35%) and bone (12%) continue to

Table 2: Number of 'physiology' publications indexed in Web of Science for the listed 'locomotion' topics from 1987-2016. Percentages are of the total number of 'physiology' publications in each topic (see Table 1).

	Physiology Publications (hundreds)			% Total Physiology Publications		
	1987-1996	1997-2006	2007-2016	1987-1996	1997-2006	2007-2016
bone	7.3	14.1	29.6	12.1%	23.3%	49.0%
cartilage	1.2	2.3	3.8	14.0%	27.0%	45.4%
ligament	0.7	1.9	3.9	10.3%	28.4%	57.2%
skeletal muscle	47.6	85.0	88.0	19.7%	35.1%	36.4%
tendon	1.7	4.6	6.9	11.6%	32.1%	47.8%
motor unit	2.2	4.3	5.4	17.5%	34.1%	42.6%
motoneuron	8.8	13.0	10.3	24.1%	35.7%	28.4%
motor nervous system	2.0	4.8	5.5	15.8%	38.2%	44.4%
locomotion	4.7	9.3	9.9	18.7%	36.8%	39.2%
walking /gait	3.7	9.1	18.7	11.0%	27.2%	55.8%
voluntary movement	2.0	4.4	5.2	16.8%	36.7%	43.5%
exercise	49.1	84.4	120.1	17.4%	30.0%	42.7%
motor control	7.9	18.2	25.5	15.1%	34.8%	48.5%

provide high proportions of the physiology papers. Together, locomotion, walking and gait provide 11% of publications.

Remarkably, total publications in many of these topics have increased at an even faster rate, so that the last ten years have seen the publication of 40-60% of total research articles. Therefore, despite the increase in physiology publications in 'locomotion', the greater rise overall has produced a slow decline in the percentage of publications attributed to physiology from 6.7% (1987-1996) to 5.3% (1997-2006) to 3.9% (2007-2016; see Fig. 2). Physiology has held reasonably steady for some 'locomotion' topics (bone, ligament, motor unit) but has fallen for skeletal muscle and exercise, which comprise the bulk of physiology papers.

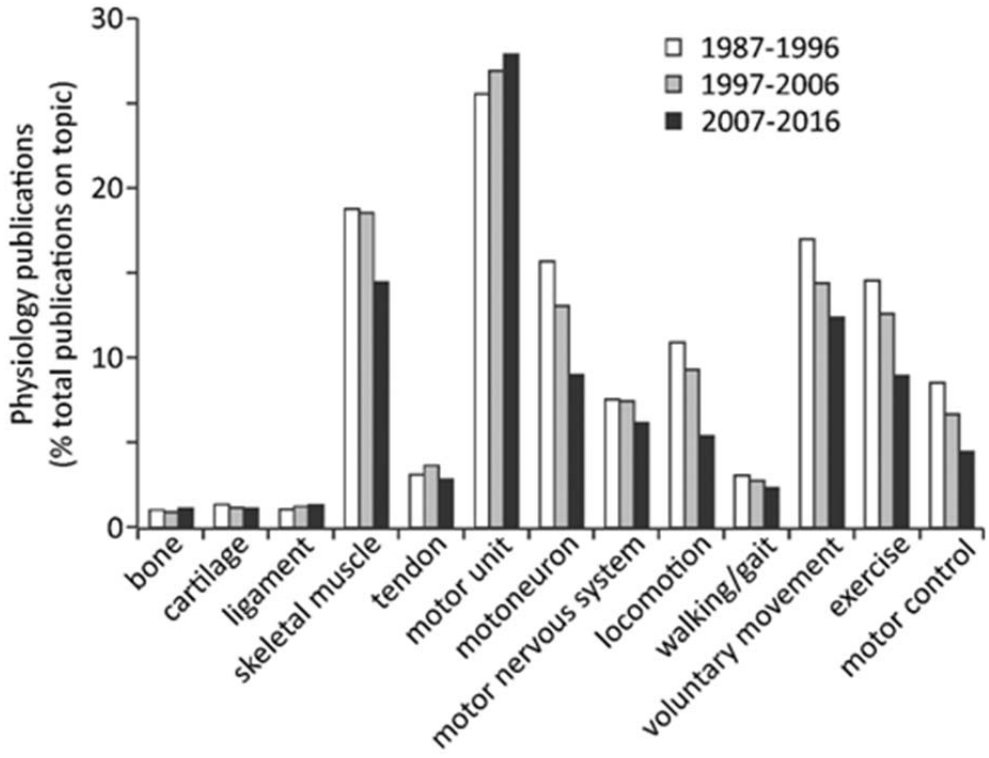

Figure 2. Web of Science publications designated to be in the research area 'physiology' for the searched 'locomotion' topics. Number of publications per decade is displayed as a percentage of all publications on the topics. This has decreased for most topic areas.

Surprisingly, other physiology papers are increasing less quickly than those on 'locomotion' topics with only 23% published in the last 10 years. Hence, the proportion of physiology papers identified as 'locomotion' topics has steadily increased from ~14% (1987-1996) to ~22% (1997-2006) to ~25% (2007-2016).

With the apparent relative decline in physiological research, what areas dominate in research into the musculoskeletal system and its control? For the last ten years, neurosciences/ neurology is the research area with the highest representation (10.8%) in the chosen 'locomotion' topics. However, this area has not risen substantially over the past 3 decades. Areas in engineering and technology (Engineering, Science technology other topics, Material science) all show large increases. Summed together, these technology areas have increased from 6% to 9% to 16% across the decades. The human oriented fields of Sport Sciences and Orthopedics show small increases (<1% per decade), as does Cell Biology.

Trajectory of publication over the past ten years

Within the past decade the number of publications per year on 'locomotion' topics has risen by >50%. The numbers of physiology publications has remained steady whereas other research areas have increasing numbers of publications (Fig. 3). Therefore, physiology has declined in its representation from 4.8% to 3.2% of 'locomotion' topic papers from 2007-08 to 2015-16. The most dramatic increases in papers are in Science Technology Other (1.6% to 6.0%) and Research Experimental Medicine (2.8% to 4.1%). For areas such as Neuroscience, Orthopedics and Sport Sciences increases in publication numbers of 26-44% were not sufficient to maintain a steady percentage of the total publications in 'locomotion' topics.

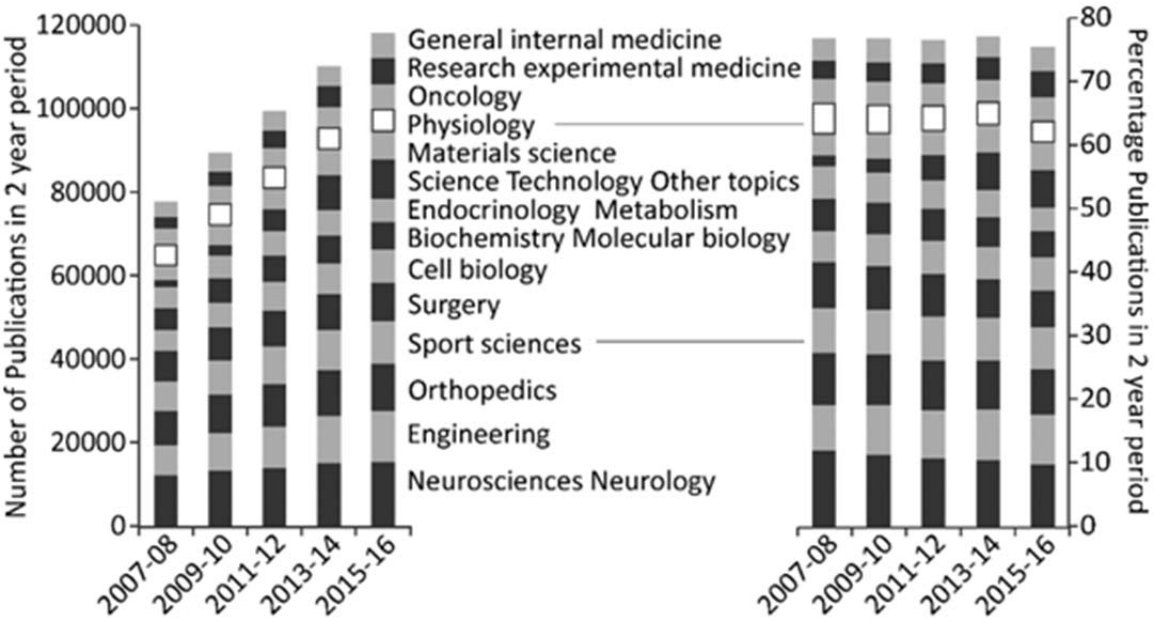

Figure 3. Number of publications on 'locomotion' topics from different research areas (Web of Science) in 2 year periods from 2007-2016. The top 14 research areas are included. The graph on the left shows the number of publications in each research area. The graph on the right shows the same data as percentages. Note that 'physiology' publications (white) remain steady in number but decrease as percentage of the total.

Skeletal muscle and exercise are two topics where physiology accounts for a relatively high percentage of publications. For the skeletal muscle topic, physiology publications per year declined over the past decade from 990 in 2007 to 838 in 2016. In contrast, total publications in the area increased by ~30%. Hence, the percentage of physiology publications fell from ~18% in 2007-08 to ~12% in 2015-16. For exercise, physiology publications rose by 21% but total publications rose by 83%. Thus, this topic also shows a drop in the percentage of physiology publications across the decade from ~11% to ~7.5%. Indeed, a relative reduction in the prominence of physiology across the past decade is a common feature across all the topics searched.

What does the decrease in the percentage of published papers identified as physiology mean?

For Web of Science, the research areas of articles are derived from the journals in which the articles are published. That is, each journal is designated to belong to one or more research areas. For physiology, 87 journals are currently designated as 'physiology'. Surprisingly, 'locomotion' articles in the subject area of physiology have been published in 163 sources in the past decade. It is not clear whether this reflects changes in journal categorization over the decade or whether articles from sources other than journals (e.g. books/ book series) are included. Nevertheless, for 2-year periods over the decade, the number of relevant sources varied between 83 and 111 with no consistent trend over time. However, closer examination of article numbers in each journal shows decreasing publication numbers in some established journals such as the Journal of Physiology, the Journal of Applied Physiology, and the American Journals of Physiology with increasing numbers in other journals, such as Frontiers in Physiology, Cellular Physiology and Biochemistry, and International Journal of Sports Physiology and Performance. The European Journal of Applied Physiology, Applied Physiology Nutrition and Metabolism (previously the Canadian Journal of Applied Physiology) and the Journal of Neurophysiology have held relatively steady. For the journals that are publishing fewer 'locomotion' articles, this decrease appears to be an overall decrease in articles published rather than a specific decline in the topic areas.

The mix of journals in which the top 25 authors (by number of publications in the area) publish has broadened between 2007-08 and 2015-16. In each period, the top 25 authors published 265 articles. In 2007-08 >90% of the publications were in 11 journals and in 2015-16 in 17 journals. The most obvious change echoes the trends for all authors. There is a drop in the share of publications in the Journal of Applied Physiology (26 to 12%) and Journal of

Physiology (18 to 11%) with the Journal of Biological Regulators and Homeostatic Agents (established 2006) rising from 0 to 9% and Cellular Physiology and Biochemistry (est. 1991) from 0 to 4%. The open access general physiology journals, Frontiers in Physiology (est. 2007) and Physiological Reports (est. 2013), have also each increased from 0 to 3%.

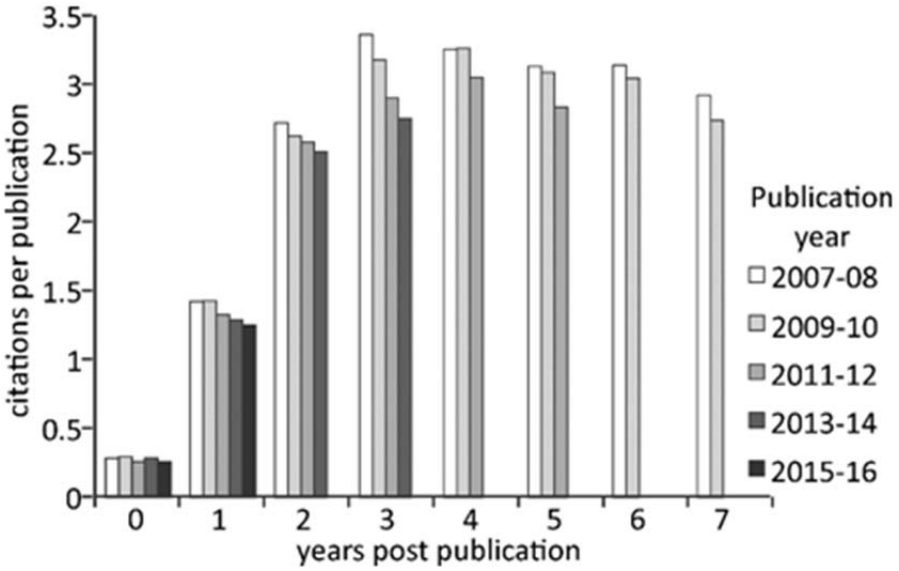

Figure 4. Citations per year per publications for 'physiology' publications published in 2-year periods from 2007-2016. Each 2-year period is represented by a shaded column. Note that year 0 goes from 2007 for 2007-08 publications (white columns) through to 2015 for 2015-16 publications (black columns). Of note is that for the same number of years post-publication, citations are gradually decreasing for more recent publications.

A particularly worrying trend is that more recent 'locomotion' physiology publications also appear to be gathering fewer citations. For example, articles published in 2007-2008 were cited an average of 2.7 times in 2009 and 3.3 times in 2010. By contrast, articles published in 2013-2014 were cited 2.5 times in 2015 and 2.7 times in 2016. Moreover, this decrease seems to be consistent across publication years (see Fig. 4). When 'locomotion' publications identified as sport sciences are analyzed in the same way, there is not a similar consistent fall in citations. Articles published in 2007-2008 were cited 2.0 and 2.8 times in 2009 and 2010, respectively, and articles published in 2013-2014 were cited 2.1 and 2.5 times in 2015 and 2016.

It is difficult to identify what underlies the plateau in publications in the physiology of the musculoskeletal system over the last decade, and the apparent drop in citation rates is even more difficult to explain. The number of physiology journals is stable and this could underlie the stable number of publications attributed to physiology. However, other areas have seen increases in publications without increases in journal numbers.

Data from the National Institutes of Health (NIH; 30) show two trends in funding over the past decade for physiology research (identified by the medical school department from which applications originate). First, the number of applications decreased by ~10% from 2007 to subsequent years and second, the percentage of applications funded also decreased. Together, this means that ~20% fewer physiology grants were funded in 2015-16 compared to 2007-08. That is, ~200 per year compared to ~250 per year (Fig. 5). By comparison, neurosciences

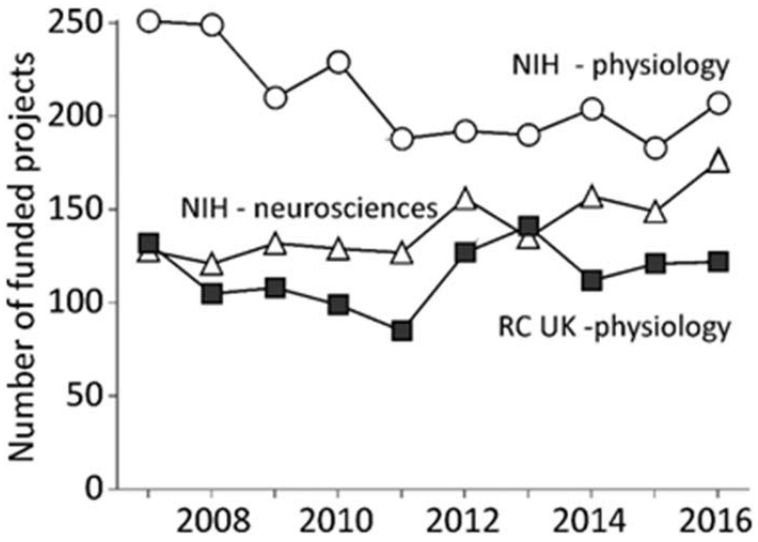

Figure 5. Number of research grants funded each year (2007-2016) by National Institutes of Health (NIH) and Research Councils UK (RC UK). NIH grants were identified by the medical school department from which applications originated. Physiology (white circles) and neurosciences (white triangles) are graphed. RC UK grants were identified by the search term 'physiology'.

applications have increased by ~50% across the decade with funded grants increasing by ~38%, although the number funded in 2016 (176) remains lower than for physiology (207).

For the UK, data from Research Councils UK (37) show that research grants identified by the search term "physiology" decreased from 132 in 2007 to 85 in 2011 but then recovered over the past 5 years to 122 in 2016. Over the same time, total research grant numbers also fell from 2007-11 and then partially recovered, so that physiology grants have become a slightly higher percentage of the total (2.9% in 2007-08 to 3.8% in 2015-16). Thus, based on the number of funded research grants, the U.S. and U.K. data suggest that physiology funding started at a high ~ten years ago, went through a particularly bad period and has started to recover over the last 2-4 years.

Finally, what of falling citations? This essay began with a brief overview of the field based on highly cited papers from the past 5 years. These papers were identified by Web of Science as "highly cited" or "hot", but were not selected on their automatic identification as physiology papers. Rather, they were selected based on my personal opinion that they were "physiology" with subject matter relevant to the musculoskeletal system and its control. From this idiosyncratic selection of ~120 papers only 10% would be identified as physiology from their publication source. Some 20% of the publications came from generalist journals, while the others were from specialist journals. This suggests that many well-cited papers that could be classified as physiology are missed in the wholesale assignment of journals to research areas.

Difficulty in identifying research as physiology is not necessarily a problem for progress in understanding 'locomotion' or the musculoskeletal system and its control, as it is the

substance of research that is of interest to scientists rather than the way it is categorized. However, it may mean that the discipline of physiology may be undervalued.

Conclusion

It is an exciting time for the musculoskeletal system. We are starting to understand how factors released by the musculoskeletal tissues underlie the benefits of exercise across many organs and also how these molecules are linked to ageing and disease both of musculoskeletal tissues and throughout the body. Advances in neuronal imaging and optogenetic techniques are putting together the neuronal circuitry for movements from locomotion to reach and grasp. While many details remain unknown in each area, large challenges also remain in translation of findings from cell and animal models to human health and finally prevention or amelioration of human disease.

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The Post-Genomic Cardiovascular/Respiratory Physiology Will Go More Diverse but Necessitate Multi-levels of Integration based on New Technological Innovations

Ryuji Inoue*

Department of Physiology

Fukuoka University School of Medicine

Nanakuma 7-45-1, Jonan-ku, Fukuoka 814-0180, Japan

*Chair of the International Union of Physiological Sciences, Commission II-Circulation & Respiration

Address for correspondence:

Dr. Ryuji Inoue

Professor and Head

Department of Physiology

Fukuoka University School of Medicine

Nanakuma 7-45-1, Jonan-ku, Fukuoka 814-0180, Japan

Email: inouery@fukuoka-u.ac.jp

Running Head: Post-genomic cardiovascular/respiratory physiology.

Abbreviations: ASC: apoptosis-associated speck-like protein containing a CARD

NLPR3: NOD-like receptor family, pyrin domain-containing-3

Abstract

After the complete sequencing of whole human genome, vigorous efforts have been devoted to deciphering the enigma of life and disease from a viewpoint of gene- or molecule-based functionalities. As the consequence, new and diverse knowledge is being deposited at an unprecedently rapid pace, culminating in formation of intractably huge databases. The cardiovascular/respiratory physiology is not an exception of this trend as seen in the major strategic visions for bioscience of many leading research institutions in front-runner countries. However, such flood of information simultaneously necessitates, in addition to enormous power of super-computation, new optimal concepts/logics and methodologies/technologies whereby to integrate the data accumulated at multiple functional levels from molecules to whole body. In particular, the tissue/organ-level theory and methodology seem most seriously lacking. This short essay attempts to overview what has been achieved so far in our field in last one and half decades, and to provide possible future directions to go, which will probably rely on innovations in intravital imaging modalities, development of new tissue/organ engineering techniques or bio-fabrications, and active utilization of systems biology approaches.

Key words:

Genome-based Medicine, Tissue/Organ Logics, Intravital Imaging, Bio-fabrication, Systems Biology

Current Research Status

Post-genomic study prevails in cardiovascular/respiratory physiology and medicine

The basic research of cardiovascular (CV) and respiratory (RS) medicine in the post-genomic era, like in the other fields of bioscience, has focused on elucidating how genomic information is translated into organismal functions, individual behaviors and diseases, by combing the molecular biological methods with the phenotyping or functional analyses of transgenic animals and animal disease models. Consequently, huge databases cataloging the linkage of genes to cellular-to-whole body functions and vulnerabilities to diseases have been created and are now available for contemporary and future research uses (e.g. Mouse Genome Informatics; 43). At the time of writing, there are more than 11,000 and 8,000 entries by quick key word search with 'CV' and 'RS' respectively. Along with this is active identification of causative genes or chromosomal loci for human Mendelian-type or rare diseases by gene-linkage analyses, whole- genome screen and exome-sequencing, and their vast information are deposited in the OMIM-catalog (e.g. long QT syndromes: 75 entries, familial cardiomyopathies: 744 entries; 44). More recently, efforts have been devoted to elucidating the complex genetic background for common CV diseases (CVDs) and RS diseases (RSVs) such as hypertension, atherosclerosis, coronary artery disease, myocardial infarction, heart failure, asthma, chronic obstructive pulmonary disease (COPD), by means of large cohort surveys of human genome polymorphisms (SNPs) and concomitant functional analyses (GWAS-catalog[45]) in conjunction with studies on epi-transcriptional and post-translational modifications as well as various levels of 'omics' studies (e.g. TOPMed program; 46), with the aid of powerful bioinformatics and computational tools.

Chronic inflammation is critical for the pathogenesis of CVDs and RSVs

From quite a different viewpoint against this enthusiasm for the 'genotype-phenotype' paradigm, however, more complex and intricate mechanisms have gained attention as for the pathogenesis of common diseases. It is well recognized that common diseases such as diabetes mellitus, heart failure (34), atherosclerosis (36) and COPD (2) follow long progressive time courses over the whole life span. These highly prevalent diseases involve a series of pathological events evoked/promoted by environmental factors comprised of the onset and sustainment of inflammation and subsequent tissue remodeling processes manifested as hypertrophy, degeneration, fibrosis or calcification, thus being classified as 'inflammatory diseases'. There are numerous factors/mediators identified to initiate/promote/modify the transition from inflammation to pathological remodeling, including a variety of cellular stresses [oxidative stress or reactive oxygen species (ROS), carbonyl stress or reactive carbonyl compounds (RCOs), nitrosative stress, reactive cysteine persulfide, mechanical stresses, etc.], migrating immune cells, pro-/anti-inflammatory cytokines and the other bioactive mediators. For example, sustained hyperglycemia (e.g. in diabetes mellitus) has been shown to increase both oxidative and carbonyl stresses inducing various cardiac and vascular dysfunctions and remodeling. This occurs through very complex and interwoven signaling pathways involving non-enzymatic formation of advanced glycation end-products (AGEs) [and lipooxidation end-products (ALEs)] and activation of their specific receptors (RAGEs) present on all cells relevant to the atherosclerotic process (macrophages, endothelial cells, and smooth muscle cells), which results in the induction of oxidative stress and proinflammatory responses, and activation of other biochemical cascades involving PKC, p38MAPK, fetuin-A, TGF-β, NF-κB, ERK1/2 (1, 22).

Emerging concepts and subdisciplines for CV/RS physiology/pathophysiology

Further complexities are added to the pathogenesis of inflammatory diseases by the discovery of newly-emerging mechanisms that modulate inflammation/remodeling responses in various

ways:

(1) ‘Inflammasomes’ play active roles in both pathogen-initiated and sterile inflammations which are caused by damage- or danger-associated molecule pattern (DAMPs) derived from damaged tissues or exobiotic agents (e.g. silica, cholesterol crystals). The canonical signaling pathway downstream of inflammasomes includes the NLPR3/ASC/caspase-1 complex, activation of which facilitates the production of IL-1β to cause cell death contributing to atherosclerogenesis, myocardial infarction and other CVDs and RSVs (>400 Medline hits for 2 years and 3 months;30)

(2) Perivascular adipose tissues (PVAT) actively release numerous bioprotective/biotoxic factors (adipokines, adiponectin, leptin, prostanoids, NO, hydrogen sulphide, palmitic acid, miRNAs, etc.) and contribute to the pathogenesis for CVDs (e.g. coronary artery disease via increase oxidative stress, angiogenesis, vascular remodeling etc.), but also to beneficial vasodilative actions to maintain the patency of vein grafts, in part via NO release and adipocyte-derived relaxing factor (ADRF)-mediated K channel activation (>100 Medline hits for 2 years and 3 months; 9)

(3) Mitochondrial dysfunction is known to impair intracellular energy metabolism and increase oxidative stress via ROS production via uncoupling of electron transfer chain, and associated with numerous CV and RS dysfunctions. However, recent studies provide different lines of evidence that impaired mitochondrial dynamics, which occurs through defective mitochondrial fusion, fission, biogenesis or mitophagy, causes a broad spectrum of CVDs and RSVs (>5000 Medline hits for 2 years and 3 months; 29,41).

(4) Autophagy plays essential roles for cell/tissue homeostasis maintenance by removing damaged organelles. Many of age- and oxidative stress-related CVDs and RSVs (myocardial infarction, cardiac hypertrophy, diabetic cardiomyopathy, atherosclerosis, hypertension, asthma, COPD etc.) are tightly associated with the defective autophagy, and often involve the

impairment of mitochondrial dynamics (>1500 Medline hits for 2 years and 3 months; 29,31).

(5) Non-coding RNAs (miRNAs, long non-coding RNAs, circular RNAs) critically contribute to cardiovascular function via epigenetic control and serve, when abnormally increased and released to the circulation, as biomarkers for risk stratification, diagnosis and prognosis of many CVDs and RVSs (>2000 Medline hits for 2 years and 3 months;35).

(6) Exosomes are secreted from almost all types of cells and serve as a cargo safely delivering proteins, enzymes, lipids and miRNAs to distant recipient cells to regulate a variety of physiological functions. Under pathological conditions, abnormally released exosomes cause CVDs as well as RVDs exemplified by the progression/metastasis of lung cancer, hypersensitivity of airways (via exosomes of microbacterial origin), and myofibroblast trans-differentiation in COPD (>200 Medline hits for 2 years and 3 months;4).

(7) The gut harbors trillions of bacteria which interact with adjacent cells in a symbiotic relationship called ‘microbiome’. Gut microbiomes modify the intestinal immunity and metabolism and affect a wide range of physiological and metabolic processes of the body, and their imbalance (‘dysbiosis’; induced by foods, drugs and diseases) can produce various CVDs and RSDs. A noteworthy pathogenic mechanism associated with microbiomes is the production of a toxic metabolite trimethylamine-N-oxide (TMAO) from dietary phosphatidylcholine and L-carnitine, the elevated serum level of which correlates well with the aggravation of atherosclerotic lesion via suppression of reverse cholesterol transport in macrophage, liver and intestinal cells, thus increasing the risk of coronary artery disease. The microbiota dysbiosis in the lung, which can influence its host defense and immunity, may also be causally related to the pathogenesis and exacerbations of chronic lung diseases, i.e. asthma, COPD, cystic fibrosis, and idiopathic pulmonary fibrosis. A new notion of ‘vascular’ microbiome in diseased blood vessels is emerging as another potential pathomechanism for atherosclerosis, aneurysms and vasculitis (>1200 Medline hits for 2 years and 3 months;

7,18,27,31).

The above list is continuously expanding to generate further enormous complexities for the pathogenesis of inflammation. Needless to say, this flood of information is beyond our intuitive understanding and handling, necessitating the systems approaches whereby to incorporate all key players of signaling into relevant dynamical models and integrate their intricate interactions to simulate the whole system's functionality (e.g. Cell Designer, Pathway Commons; 48,49).

Innovations strongly promote physiological studies

There are many innovative advances made in microscopic research which have enabled to observe atomic-, nano- and meso-scale subcellular and intercellular structures in association to function. Several notable examples include:

(1) the atomic structures of cAMP-bound human hyperpolarization-activated cation channel and open/closed conformations of ryanodine receptor which are essential for cardiac pace-making and contraction have been resolved by the cryo-electron microscopy; 8,25).

(2) super-resolution fluorescence microscopy revealed that microdomain-targeted remodeling of L-type Ca^{++} channel properties may contribute to ventricular arrhythmogenesis in heart failure models and that cholesterol-enriched domains in the cell membrane may mediate high density lipoprotein-induced eNOS activity; two-photon microscopy-based intravital imaging is used to track the extravasation and movement of immune cells in small blood vessels; 37,39).

(3) 3D-scanning electron microscopy (e.g. FIB-SEM) has started to be applied to uncover the functional connection of otherwise unrecognizable fine 3D structures. In addition, optical

mapping with voltage-sensitive dyes and optogenetic approaches are becoming indispensable tools to investigate the multi-dimensional mechanisms for cardiac action potential propagation and (reentrant) arrhythmias in the heart and neurovascular coupling and control of heart and blood vessels; 40).

For the whole animals or human subjects/patients, several important imaging modalities have been widely used to monitor the intact organ function in situ (e.g. cardiac motion and myocardial flow), by echography, CT, MRI and PET/SPECT. However, novel technologies (high resolution MRI, Diffusion tensor MR etc.) are emerging that can probe the mesoscale structure and local functional dynamics, quantifying the anatomical-functional variability in health and pathology (e.g. myocardial infraction), many of which are evolving toward the personalized clinical use (24). It is important to emphasize again that all these functional data will be ultimately utilized to construct comprehensive computer models based on realistic anatomy to better understand and explain how central and local (hemo-)dynamics work to regulate respective organ functions. Of particular note, recent computational modelling of cardiac electrophysiology is evolving successfully toward integrating these functional imaging data with other experimental findings from expression systems and animal models and developing novel testable hypotheses.

Regenerative medicine will require more physiological research

The advent of inducible pluripotent stem cell (iPSC) technology is one of most epoch-making advances in CV (and perhaps RS) regenerative medicines. It is becoming increasingly realistic that dysfunction of damaged tissues and organs can adequately be replaced or compensated by regenerated tissues/organs, or those engineered on artificial scaffolds/devices. Although no such clinically useful applications yet exist for the heart, blood vessels and the

lung, transplantation of iPSC-derived cardiac tissue sheets consisting of cardiomyocytes and vascular cells has paved a new avenue to the unprecedented regenerative therapy of infarcted hearts (28). iPSC-derived cells also allow benchtop investigation of complex patho-mechanisms underlying human cardiovascular diseases such as arrhythmias (16) and facilitate the effective screening of cardiotoxic or new anti-arrhythmic compounds by automated analyses, the information of which can further be used to construct *in silico* models to select and validate drug candidates (6,11,32,42).

Beside their use as regenerative resources, iPSCs overexpressing miRNAs with anti-inflammatory and/or immunomodulatory actions can be applied in the proximity of damaged cells/tissues, or iPSC-derived exosomes containing bioactive proteins and lipids can be delivered to recipient cells to alleviate local inflammatory/immune reactions sustaining in diseased tissues such as infarcted myocardium and atherosclerotic lesions (19). Despite these enormous therapeutic potentials in clinical practice, our physiological and pathophysiological understanding about how iPSCs exert such beneficial effects on damaged cells/tissues is still premature. In this regard, this emerging field should become one of the major targets of future physiological research.

Another stream of modern physiology – holistic approach

Entirely opposite to the large-scale, cutting-edge research trends described above, another stream of physiological research holistically views health and disease as the continuum. This type of physiology aims to investigate the practical aspects of or apply the basic principles of physiology to health promotion and disease prevention rather than direct treatment of diseases, and is becoming a non-trivial subspecialty of cardiovascular and respiratory physiology in the post-industrial era. In particular, the notion of ‘Mibyo’ (‘not yet ill’ in

Japanese), which originally came from the eastern traditional medicine, has received growing attention as an unprecedented clue to understanding the pathogenesis, preventing the onset or even reversing the course of diseases. In the modern definition, 'Mibyo' represents a pre-symptomatic or preclinical state without any subjective complaints but with objective abnormalities associated with e.g. obesity, hypertension, borderline diabetes mellitus, gout, non-symptomatic cerebral infarction, non-ruptured arterial aneurysm, latent heart failure, and fatty liver (47). For example, oxidative stress, the major cause of CVDs, is thought to increase depending on sex, high-calorie, high carbohydrate diet, short sleep, smoking, alcohol and stress, and improving these risk factors is believed to reduce the oxidative stress. There are numerous such physiological studies, and it is an important issue of intense investigation how transition from pre-symptomatic to symptomatic states can be prevented or decelerated by health-promoting regimens such as aerobics, yoga, calorie restriction, and regular dietary intake of polyphenols, anti-oxidant herbs and phytochemicals. The proposed mechanisms so far suggest the common involvement of anti-oxidant, anti-inflammatory and anti-ageing reactions such as activation of eNOS and induction of sirtuins (47). Importantly, the pathophysiological research on pre-symptomatic state is now getting correlated with the comprehensive study of genetic variability (SNPs) annotated with phenotypic traits, which are being profiled in large public databases ('big data') and could be used in future to detect the pre-symptomatic state to prevent the onset of illness by active medical interventions. And early warning signals for critical transitions from pre-symptomatic to diseased states could be predicted by combining both appropriate biomarkers and theoretical approach (23).

Finally, as the globalization and diversification of life style and other activities proceed, the new frontiers are emerging for the CV/RS physiology. This is related to the ethnicity, environment (climate, altitude, temperature, humidity, air pollution, etc.), culture, profession,

sports, travelling, individual habits and preferences etc., creating many interesting subspecialties of physiology which meet the needs of the times. Note that the 'extreme' CV/RS physiology at the Himalaya mountain (high-altitude physiology) is an interesting topic of plenary lectures in the 2017 Rio meeting!

Interestingly, some of these emerging new physiological sub-disciplines appear to be intimately associated with various innate rhythms of whole body, organ or cellular activities such as circadian rhythm, and may reflect, to considerable extent, the periodic changes of nerve activities (autonomic tones), as found in the condensed incidence of myocardial infarction, asthmatic attack, and some arrhythmia in specific time zones of the day (12). This new category of biology, called 'chronobiology', will provide a new investigational framework for normal physiology and human disease (38).

Future perspectives

Although there is little doubt that physiologists-initiated research will continue to underpin the whole bioscience by discovering the new basic principles of life, social requests and the funding status will prompt the physiology of next post-genomic decade to go with governmental strategic visions known as the 'precision medicine'(50) or 'personalized medicine'. As recently announced in the strategic initiatives of major research institutions in several frontrunner countries (NHLB, MRC, ERC and AMED; 51-54) clear timelines and goals have been set to accomplish the selected research priorities represented by the key words, innovation, resilience, repair and replacement. The essence of resilience would lie in the reversible continuum between health and disease, and one of the missions of future medicine will be to understand how resilience to disease develops and breaks down and to discover the way to prevents it by appropriate medical interventions. The mechanisms for

Mibyo, ageing and frailty could be interpreted in similar contexts. Thus, the future direction of physiological research will be not simply to discover the new logics and principles governing normal biological function across all hierarchical levels of the body (from molecules through organ functions to behaviors/environmental adaptations), but to re-integrate them in such a way of reconstructing a realistic multi-scale, multi-physics system that can reproduce the continuum of health and disease, thereby contributing to the personalized medicine and health promotion. This difficult mission will be exactly the ultimate goal of 'physiome' projects (33,55-58) running in several international collaborations. To promote this 'mission impossible', we probably have to: (1) accumulate multi-dimensional functional data using innovative technologies; (2) develop the recording modalities enabling detailed functional monitoring/profiling of both healthy subjects and patients on daily basis (e.g. via mobile or wearable devices) and garner the data with them; (3) evolve the advanced bioinformatics and systems physiology and improve the high-performance computing power so as to pertinently interpret the various levels of physiological data and organically integrate them with the fruits of genomic medicine such as the 'big data' obtained from 'trans-omics' studies as well as new findings from regenerative medicine (33). This will be further accelerated by constructing international networks of bioscience platforms freely accessible by researchers for active use (e.g. Garuda Alliance; 59), and by exploiting mobile medical devices/applications that connect healthy subjects/patients with remote medical services via the IoT technology (e.g. smart phones) and allow real-time sampling and diagnosis of personalized functional data (e.g. Pathway OME; 60).

As such innovative tools, a remarkable progress is being made in the quality and application of intravital recording modalities, exemplified by; motion vector prediction method for a high-speed, high-resolution tracking of cardiac motion (MVP); super-resolution optical

fluctuation imaging for flow dynamics monitoring in microcirculation (SOFI); photo-acoustic imaging for small blood vessel diameter measurement; deep-tissue imaging or stimulation modalities using near-infrared (NIR) light such as diffusive optical tomography (DOT) and nano-particle activation technique based on photon upconversion; ultra-thin, deformable, high-resolution multiple-electrode array for minimally-invasive electrophysiological recording (NeuroGrid; 3,10,13,15,18,21). All these new modalities will enable to monitor or elicit dynamic functional changes in small localized regions of various visceral organs, thereby providing unprecedented new information about the complex reactions occurring *in vivo*.

In my personal view, the physiological research in coming years will bifurcate into two directions, i.e. 'generalized' approach covering the full spectrum of 'average human' life which is tightly combined with large-scale biologic databases, and 'personalized' or 'individualized' approach which does not aim at the 'one-size-fits-all' principle and is tightly linked with individual variability in all aspects that determine each self. These two opposite approaches would not be exclusive but rather complementary helping each other to foster more exact understanding about the life. There is however a huge gap of knowledge left between molecular/cellular and whole body levels. One promising approach to fill in this gap may be a 'reverse' or 'synthetic' physiology in which cells are used to re-build functioning tissues and organs by means of bio-fabrication technologies. In fact, 3D-bioprining has been successfully applied to create visceral organ-mimetics of blood vessel, trachea and heart or to construct heart tissue on a chip device (14,26,33). These artificially constructed tissues/organs could be, in addition to their ultimate use for replacement therapy, extremely instrumental to pursue the tissue/organ-level logics and principles governing their functions. In either case, physiologists will have many different thrilling options for their future research,

which should be navigated by their own genuine scientific curiosities and motivations.

Acknowledgements

I am grateful to colleagues in my lab and section chairs of the Commission II, Profs. GA. Meininger and T. Kuwaki for helpful discussions.

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Future Perspectives of Secretion and Absorption Processes in Health and Disease

Rene Bindels*

Department of Physiology

Radboud University Medical Center

Nijmegen, PO Box 0910, 6500 HB

The Netherlands

*Chair of the International Union of Physiological Sciences, Commission V-Secretion & Absorption

Corresponding author:

René J.M. Bindels,

Department of Physiology,

Radboud University Medical Center,

Nijmegen, PO Box 0910, 6500 HB, The Netherlands

Email: Rene.bindels@radboudumc.nl

Telephone +31-24-3614211

Running Head: Future perspectives of secretion and absorption processes

Physiological relevance of secretion and absorption processes

Secretion and absorption are physiological processes carried out by epithelial cells present in for instance the kidney and gastro-intestinal tract. In general, secretion encompasses the cellular release of ions and molecules to the external environment of the cell. This can be achieved by exocytosis, by transport of the substances across the plasma membrane or by simple diffusion through the lipid bilayer of the plasma membrane. For example, endocrine cells secrete hormones that subsequently enter the bloodstream or epithelial cells in the pancreas secrete digestive enzymes into the digestive tract to facilitate the digestion. Thus, secretion moves material from the extracellular space to the lumen of the kidney or gastro-intestinal tract. Conversely, absorption is the transfer of substances from the lumen of the kidney or gastro-intestinal tract to the extracellular fluid. In the gastro-intestinal tract absorption follows the digestive process of nutrients. This can be achieved by endocytosis, by transport of the substances across the plasma membrane or by simple diffusion across the tight junctions. In the last decades, the underlying molecular mechanisms of the secretion and absorption process have been studied in great detail. The following arbitrary subdivision can be appreciated:

Gastro-intestinal tract

Our digestion starts by eating food and ends in general a day later by removal of the remaining waste via the stool. The digestion is facilitated by the many digestive enzymes that are secreted along the way. Nutrients from the diet are absorbed into blood across the polarized epithelial cell layers forming the small and large intestinal mucosa via both passive and active mechanisms. The mechanisms of intestinal absorption of nutrients involve sodium, anions (chloride, sulphate, oxalate), carbohydrates, amino acids and peptides, lipids, vitamins, as well as the major minerals and micronutrients. In recent years, the molecular

identity, specificity, and coordinated activities of key transport proteins and genes involved, has been resolved and can often explain the pathophysiology of acquired and congenital intestinal malabsorption, and form the basis of clinical tools to treat malabsorptive symptoms.

The kidneys

Renal physiology encompasses all functions of the kidney, including maintenance of fluid and acid-base balance; regulation of sodium, potassium, and other electrolytes; clearance of toxins; absorption of glucose, amino acids, and other small molecules; control of blood pressure; production of various hormones, such as erythropoietin; and activation of vitamin D. On a daily basis ~180 L of blood is filtered by the glomeruli and passes into the lumen of the nephrons. Here, the glomerular filtrate is eventually concentrated to ~1.5 L of urine as a consequence of the reabsorption and secretion processes. Through a delicate series of long-standing studies involving, micropuncture, *in vitro* tubule perfusion, genetic, cell biological and animal studies, the various reabsorption and secretion processes along the nephron have been unravelled. These seminal studies have greatly contributed to our current physiological understanding of electrolyte and acid-base disturbances. Above all they have shown the integrative function of the kidney in achieving homeostasis in our bodies.

Exocrine glands

Exocrine glands secrete various products including hormones, enzymes, metabolites, and other molecules which via the duct of the gland flow towards the surface to which the duct is in contact. For instance, a mammary gland produces milk to feed young offspring. In the breasts, during pregnancy when levels of prolactin, estrogen, and progesterone rise secretory alveoli develop. Milk secretion (lactation) begins a few days after birth, caused by reduction in circulating progesterone and the presence of prolactin, which mediates further

alveologenesis and milk protein production and regulates osmotic balance and tight junction function.

Future perspectives

In the last decade, a wealth of information has been obtained about the molecular mechanisms regulating the various secretion and absorption process in the body. This has been fueled by the genomic area disclosing ample new genes and by their subsequent physiological characterization. Most transporters have been identified which are instrumental in the individual secretion and absorption processes, their tissue distribution has been unraveled and importantly the molecular players of the signaling pathways controlling their activity have been disclosed.

In the coming area, several scientific avenues based on new technical developments will be pursued to further broaden our physiological knowledge. For instance, single cell omics will be a new frontier in physiology which could have important implications for further unraveling the molecular mechanisms regulating secretion and absorption processes. Single cell omics methods will shed new light on these processes by recognizing the heterogeneous nature of the cell populations composing the various epithelia involved. In addition, the recently established technique of growing organoids from stem cells will revolutionize our knowledge of human physiology. Organoids are clusters of cells that organize themselves into mini versions of their respective organs. They can be grown from stem cells when the precise conditions to keep them alive outside the body are applied. Organoids were first made from intestines but have since been made for many other tissues, including liver, brain and kidney. Organoids will allow scientists to better study the development and diseases of organs. Organoids have several advantages over existing approaches. They can be maintained

for months and provide an unlimited supply of material for study, meaning fewer animal studies are required. Making organoids from patients also raises intriguing possibilities for personalized medicine. All this makes organoids an exciting new tool for researchers. Organoids will transform the way we conduct medical research, from basic understanding to drug development and personalized therapies.

In the field of absorption and secretion a major development is the recognition of the gut microbiome as a new vital organ. The human microbiome is composed of bacteria, archaea, viruses and eukaryotic microbes that reside in and on our bodies. These microbes have tremendous potential to impact our physiology, both in health and in disease. They contribute to our metabolic functions, protect against pathogens, educate the immune system, and, through these basic functions, affect directly or indirectly most of our physiologic functions. The study of the human microbiome will be furthered by technological advancements on the functional interactions between the microbiota and the host. Still a lot can be learned about the interaction of the gut with for instance the brain or the kidney. Physiology and physiologists are therefore crucial to our understanding of these systems, and the best hope for discovering novel treatments.

Related, epithelial function plays a central role in physiology for transport of substrates, salts, and water. Basically, two pathways are available: a trans- and paracellular route. The transcellular pathways have been extensively studies. Recent studies have identified claudins as critical molecular components of the tight junction forming the paracellular pathway. They determine the selectivity, permeability, and tightness. Several disease mechanisms can now be explained by the dysfunction of claudins within the tight junction. Novel insights from claudin research in the coming decade will provide tools for diagnostics and treatment and a

better understanding of the pathophysiology and clinics of diseases related to malabsorption or secretion.

For exocrine physiology future areas of research will include exocrine gland development, regenerative approaches, functional relevance of salivary proteins, membrane functions in exocrine glands, understanding the aetiology of autoimmune disease, and targeting inflammation to retard disease pathogenesis. Likewise, details of exocytotic and endocytotic process in beta cells of the pancreas can now be studied at the single vesicle level through a variety of new approaches including combined electrophysiological and imaging techniques. These are exciting future possibility that may contribute to our knowledge of the pathophysiology of type 2 diabetes in humans.

Thus, the newly developed technical approaches will revolutionize both fundamental physiology as well as our understanding of disease, and technologies involved in translation to medicine. A better health outcome for humanity will benefit from translational physiology. This will, however, require an increased interaction between physiology and other disciplines to promote basic findings to the clinic and *vice versa*, and will make physiology an even more exciting and important area of research.

Molecular and Cellular Physiology Meets Big Data: Current Status and Future Directions

Jens Rettig*

Institute for Physiology und Center for Integrative Physiology and Molecular Medicine

Saarland University

Building 48, 66421 Homburg

Germany

*Chair of the International Union of Physiological Sciences, Commission VI-Molecular & Cellular Physiology

Address for correspondence

Jens Rettig

Department of Cellular Neurophysiology

Center for Integrative Physiology and Molecular Medicine (CIPMM)

Saarland University

Building 48, 66421 Homburg, Gemany

Phone: +49 6841 1616400; Fax: +49 6841 1616402

Email: jrettig@uks.eu

Running Head: Essay on molecular and cellular physiology

Keywords: Molecular physiology, cellular physiology, bioinformatics, genome, RNA editing

Molecular physiology, cellular physiology, bioinformatics, genome, RNA editing

Physiology aims to understand and explain the function of entire organisms like humans and their individual organs. While in early times functional investigations were mostly restricted to more descriptive terms, the introduction of molecular biology and the availability of cellular model systems in the middle of the last century allowed physiologists to precisely determine the contribution of individual proteins and molecules to cellular function. Subsequently, transgenic animal models were generated to transfer this knowledge into organisms to elucidate the contribution to organ function and organism behaviour. For physiology, this revolutionary approach led to the development and growth of sub-disciplines like molecular biology, cell biology and neuroscience.

Currently, another revolution in physiological research is taking place. The revolution started with the sequencing of the human genome that was completed more than a decade after its initiation in 1990 (1). We began to understand that although there is a surprisingly low number of coding information within our genome, many genes exist in many different variations, thus also generating a large complexity on the protein level. Thanks to the evolution of technological developments the entire genome of human cells is now sequenced within a few hours and allows physicians to examine patient material for potential genetic defects. In addition, new disciplines like bioinformatics and epigenetics generate a huge amount of data about the modification of genetic information of organs, cells and even subcellular compartments on the DNA as well as on the RNA level (2). As a consequence, physiologists have access to a plethora of data about the current status of functional units. The resulting challenges for physiologists in the future are manifold. This may best be illustrated by an example: RNA editing of CAPS, a protein involved in neurotransmitter and hormone release (3), results in an amino acid exchange that alters its binding affinity to another protein. Editing is tissue-specific, occuring at a frequency of 70% in chromaffin cells

of the adrenal gland and only at a frequency of 15% in the brain. The physiological consequence of this selective amino acid exchange is a 50% increase of adrenaline, a hormone that increases heart rate and regulates blood pressure (4). Mutant mice carrying this edited CAPS protein are leaner than their wild-type counterparts and show an increased physical activity. Thus, a single point mutation in a single protein expressed in a single organ leads to entirely different behaviour and appearance of the entire organism. Therefore, physiologists in the future have to consider the source, physiological condition, age and many more parameters under which genomic, bioinformatic and epigenetic data were obtained.

The balancing act between having an enormous amount of data available and bringing them into a physiological context of organ and organism function will certainly shape the field of molecular and cellular physiology for the next decades. It should be an exciting journey.

Grants

Work in my lab has been funded through the Deutsche Forschungsgemeinschaft (CRC 894).

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Professionalization of Physiology Education Activities

Robert G. Carroll*

Department of Physiology

Brody School of Medicine, East Carolina University,

Greenville NC USA

*Chair of the International Union of Physiological Sciences, Education Committee

Email: carrollr@ecu.edu

Running Head: Physiology Education

Address for Correspondence:

Robert G Carroll, PhD.

Office of Medical Education, 2N-64C

Brody School of Medicine

East Carolina University

600 Moye Blvd.

Greenville NC 27834-4354 USA

Abstract

Changes in physiology education are being driven by outcomes-based evidence documanting the benefits to learner-centered instructional methods. The learning environment no longer consists of a lecture hall, and the goal is no longer the transmission of information. Physiologists are at the leading edge of developing and disseminating pertinent educaitonal research, using both regional workshops with a facuclty development theme and using the journal *Advances in Physiology Educaiton.* The International Union of Physiological Sceinces plays an active role in promoting educaitonal activities at national and regional physiology workshops, facilitating the movement toward a learner-centered teaching model by developing the understanding and skills of the participants.

Key Words:

Faculty development, regional workshops, IUPS, learner-centered education

This is an exciting time for **physiology education and physiology educators** - embracing both the most promising and most threatening meanings of the word "exciting". The opportunities and challenges come from advances in both "physiology" and "education", as research findings into both fields continues to shape the teaching environment.

Physiology educators, particularly those in the health professional programs benefit from the integrative and foundational nature of the science of physiology. An understanding of physiology is key to understanding our health and the world around us, and is essential to the intelligent practice of medicine (3). Physiology research continues to shape our understanding of body function and consequently impacts clinical practice.

The largest expansion of interest in physiology training (at least in the USA) is driven by an interest at the undergraduate level in the benefits of health and fitness (2,8). Research in sports physiology continues to shape both the general population approaches to fitness as well as the performance of competitive athletes. The physical benefits of fitness are being complimented by research into Mind-Body Medicine (6), drawing on millennia of international expertise and practice.

Physiology is at its core a research science. Physiology is not what physiologists know, it is what physiologists do. Physiology as a core life science is ideally suited to guide the development of a scientifically literate public, particularly in the pre-college learning setting. In this era of explosive information availability, understanding the science of physiology can help individuals navigate through competing claims and data in order to make informed decisions about topics shaping the future of the individual and the world.

Physiology **educators** draw on a separate robust experimental literature – that of the science of education. The convergence of new pedagogical understanding and technological innovations has changed physiology instruction more in the past 30 years than in the century preceding that. The impact of educational technology is massive and needs to be a topic for another discussion. This essay will focus on one of the major pedagogical shifts – the move from instructor-centered to learner centered instructional approaches.

For physiologists, learner-centered instructional approaches are both familiar and challenging. Familiarity comes from our experiences in graduate and postgraduate training. Once we finished with the 'classroom' component of our instruction, we entered the ultimate learner centered environment, the research laboratory. The supervisor's role was that of a guide, a coach, and we appropriately refer to them as our 'mentor'. Responsibility for learning and mastery of knowledge, skills and attitudes resided with the student, along with the responsibility of meeting performance expectations (1).

This learner-centered experience is in stark contrast to our (40 years ago for me) learning in the lecture hall. Lectures were generally passive events, centered on transmission of information. In 1927, E.E. Slossan (7) was credited with the observation

"Lecturing is that mysterious process by means of which the contents of the note-book of the professor are transferred through the instrument of the fountain pen to the note-book of the student without passing through the mind of either."

That description unfortunately captures the lecture hall experience of many students 90 years later.

There is compelling evidence proving the benefits of active learning approaches (4). Engaging students in the lecture hall setting can be stimulated by using active learning approaches, such as think-pair-share-share activities and audience response systems. There is clear experimental evidence that active learning approaches improve both learning and retention. Some learner-centered approaches, such as problem-based learning (PBL) require significant physical and faculty resources, but specifically foster the development of self-directed, independent learners. Other approaches, such as team-based learning (TBL) and flipped classrooms, evolved specifically to address the resource limitation characteristic of student-centered learning activities.

One major challenge in the implementation of learner-centered instructional approaches lies in the lack of familiarity to both students and instructors. Changing from a familiar educational approach to a novel approach requires preparation of both the instructors and the students for their new roles. This requires both familiarity with the approaches and their limitations, as well as a commitment to change.

The real promise of **physiology education** comes from the professionalization of physiology educators. Professionalization requires more than just a commitment to expert practice. Professionalization requires physiology educators to shape and refine their activity through reflective, data-driven approaches that to contribute to the experimental literature in order to advance the field. The physiology classroom is an ideal setting for educational scholarship, as physiology instructors apply their training in experimental design to address important issues in teaching and learning.

One essential component of scholarship is the dissemination of findings. Physiology educators have significantly shaped the educational literature, particularly as reflected in the growth and impact factor of the journal "*Advances in Physiology Education*". National and international physiology conferences now include venues for poster and oral communication of educational projects, including outcomes of research in the classroom.

The program of the November 2016 regional meeting of the SAAP (South Asian Association of Physiologists) is an excellent example of the professionalization of physiology educators. As part of the conference, Dr. Rita Khadka and her colleagues organized a 1 day pre-conference teaching workshop with the theme "LEARNING OF PHYSIOLOGY IN 21ST CENTURY (WITH FOCUS ON FACULTY DEVELOPMENT). In addition, education-themed oral and poster presentations were interwoven throughout the conference. The recommendations from this conference were developed and delivered by the recently deceased Prof. Shyamal Roy Choudhury, who is greatly missed. This slate of recommendations provides a clear indication of the state of physiology education and the areas of need and growth. They are reproduced below with the permission of Prof. Choudhury.

RECOMMENDATIONS

1. The workshop recognizes the urgent need for student-centered and team - based learning opportunities for undergraduate students of Physiology.
2. The workshop recommends inquiry-based laboratories, case and problem based activities, human physiology experiments and special projects to enhance student learning and to build confidence in physiology students.
3. The Workshop recommends introduction of e-learning in physiology. The workshop

believes that curricula and course materials including teaching-learning activities, assignments and quizzes can be presented during e-learning. The workshop recommends that a set of interactive CDs to be prepared to supplement e-learning at Physiology practical.

4. The workshop recognizes the issues related to teaching of attitudes, ethical issues on biomedical research and an approach on ethical teaching for physiology educators. The workshop recommends proper orientation and training of the faculty members towards the use of various teaching-learning methodologies like (i) introducing scenario as a stimulus at the beginning of lecture, (ii) introducing Flip classroom for active learning, (iii) Real case presentation and clinical examination in lecture, (iv) development of critical thinking in lecture, (v) introducing evidence-based learning, (vi) concept mapping, (vii) Learning by Role-Play, Reflection, E-Summarization.
5. The workshop recommends the introduction of objective-structured Practical Examination (OSPE) and objective-structured Clinical Examination (OSCE) for the assessment of student's practical skills in pre-clinical and para-clinical subjects.
6. The workshop recognizes the need of developing a lesson plan which will facilitate the learning of students, stimulate higher cognitive skills of students promoting critical thinking and highlighting clinical relevance.
7. The workshop suggests that it is an integral part of faculty development to equip them with a skill of emotional intelligence through hands on workshops. This skill will help them to control and understand the emotions of themselves and the students, other faculty members, administrators, patients and attendants to be able to place themselves under adverse circumstances.

8. The workshop recommends introduction of Flipped classroom to facilitate student engagement and active learning. The workshop urges that integrated Flipped classroom to be planned if the curriculum is of integrated type.
9. The workshop urges upon the Professional Associations, such as **IUPS, APS, PS, UK, SAAP** to take steps in organizing Training Programmers/Workshops, Seminars etc. at regular intervals for promoting Faculty development in Physiology and Medical Education.

Moving forward – The Role of IUPS

The IUPS has provided active leadership in the professionalization of physiology educators. These activities began in 1983, and a teaching workshop has been held as a satellite conference of the main IUPS Congress ever since. In subsequent years, IUPS education committee has cooperated with local, national and regional groups to help organize workshops that had education themes, allowing a community of educators to flourish.

The programs of these workshops reflect the characteristics needed for the development of professionals.

1. Provide the broader physiology education community with context for educational changes rooted in research-based literature. Most of us were introduced to the classroom with little if any formal training in teaching. Our teaching approaches were mostly shaped by our positive and negative experiences as a student. One early and continuing aim of the teaching workshops is to better educate physiologists about the new approaches to teaching, including providing outcomes-based evidence of effectiveness (4).

2. Provide workshop experiences that will enhance the teaching and facilitation skills of physiologists. One major barrier to implementing pedagogical change is the lack of opportunities to experiment with novel pedagogical approaches. The teaching satellite conferences incorporate small group activities allowing physiologists to role-play both the instructor and the learner as they gain insights into novel teaching approaches.

3. Develop communities of practice. One unfortunate reality of any workshops is that implementing lasting change is difficult. As instructors return to their home institutions, competing pressures in the environment lead faculty to return to the familiar and comfortable. One way to solidify a commitment to change is to develop communities of practice (5), where shared experiences, continuing interactions and commitment to the community facilitate lasting change.

4. Identify, develop and share effective educational resources. The creation of instructional resources is expensive and most commonly occurs in the developed world. In contrast, student centered learning approaches indicate that learning resources need to be those with which the students can easily identify. Regional collaborations can identify unique educational needs, and allow the in the development and refinement of items and objects to be used in the classroom.

IUPS education Committee has a modest grant program to support these goals. The largest impact in the past 4-year cycle has been to help support regional and trans-national meetings.

Conclusion

There is a threat implied in the phrase "May you live in exciting times". The physiology learning environment is changing. In order to remain relevant, physiology educators must understand and embrace the emerging opportunities. The educational literature is guiding many of the dramatic changes that are occurring at the University. Physiology educators must consume this literature, and apply it as possible to their educational setting.

My wish for all in physiology educators is that we flourish in 'exciting' times. This requires the ability to embrace change. Educators who rely on the pedagogy of 1960 will find themselves rapidly isolated and consequently lose their effectiveness as instructors. In contrast, educators who understand and embrace change will emerge as leaders their institutional setting, and continuing to shape the experiences of our learners.

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How do Ethical Considerations Impact Physiological Sciences?

Penny Moody-Corbett[1]*, Andrea Calkovska[2], Ashima Anand[3], Pat Buckley[4], Bill Yates[5]

Northern Ontario School of Medicine, Thunder Bay, ON, Canada[1], Department of Physiology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia[2], Exertional Breathlessness Studies Laboratory, Vallbhbhai Patel Chest Institute, Delhi University, Delhi, India[3], University of South Australia, Adelaide Australia[4], Department of Otolaryngology & Neuroscience & Clinical and Translational Science, University of Pittsburgh, Pittsburgh, PA, USA[5]

*Chair of the International Union of Physiological Sciences, Ethics Committee

Email addresses:

Dr. Penny Moody-Corbett, pmoodycorbett@nosm.ca

Professor Andrea Calkovska, Andrea.Calkovska@jfmed.uniba.sk

Dr. Ashima Anand, ashima_anand@hotmail.com

Professor Pat Buckley, pat.buckley@unisa.edu.au

Dr. Bill Yates, byates@pitt.edu

Running Head: Ethical considerations in physiological sciences

Address for Correspondence:

Dr. Penny Moody-Corbett, Associate Dean Research, Northern Ontario School of Medicine, 955 Oliver Road, Thunder Bay, ON, Canada P7B 5E1, pmoodycorbett@nosm.ca,

Abstract

As physiologists we rely on careful and rigorous research methods to understand the complexities of living organisms and correct and accurate documentation in the scientific literature in order to advance science. It is understood that the research will be conducted in the most ethical fashion, maintaining the highest levels of integrity. This brief report describes the role that the International Union of Physiological Sciences (IUPS) Ethics Committee plays in providing guidance to the members of the IUPS, and a description of four topics that are often of concern in physiology and can impact physiological sciences and the credibility of the scientific record. The essay begins with an introduction by the Chair of the Committee, Dr. Penny Moody-Corbett, followed by four ethics topics: Ethical Issues in Experimental Animal Physiology, Professor Andrea Calkovska; Authorship Issues, Dr. Ashima Anand; Reproducibility and Reliability of Research, Professor Pat Buckley; and Publication Ethics and Impacts on Physiology, Dr. Bill Yates.

Keywords:

Ethics, Integrity, Animal research, Research reproducibility, Authorship, Publication

Introduction

August 21, 2001 the International Union of Physiological Sciences (IUPS), at its Council meeting in Christchurch NZ, established the IUPS Ethics Committee under the Chair of Professor Ewald Weibel, noted biologist and physiologist, University of Berne SUI. The committee at that time had 16 members, representing 15 countries. Although we are a leaner committee now of only 7 members from 7 countries, we continue to be active and engaged with Physiology and Ethics.

As you will learn in this essay, which contributes to the Compendium for the Board of the IUPS General Assembly, issues of ethics are always a concern in conducting physiology research and the best research is that which adheres to the highest ethical standards. Our essay includes three topics of on-going concern to our committee: ethical handling and care of animals in physiological experimentation, understanding the responsibilities that come with being an author and current ethical issues in physiology publications.

We begin with a brief outline of the mandate of the Ethics Committee and the highlights of the Ethics Symposia that have been part of the IUPS Congresses since 2001.

The mandate of the Ethics Committee is to provide expertise and guidance to Council in the areas of human and animal ethics as they relate to physiological sciences. The Committee is called upon to contribute to the Council for International Organizations of Medical Sciences (CIOMS) and the International Council for Laboratory Animal Science (ICLAS), to review guidelines for these and other organizations and to contribute to the quadrennial IUPS Congress. In addition, committee members contribute within their Societies on topics of ethics and physiological sciences.

A major role of the committee is to contribute to the dissemination of knowledge on topics of ethics to members of the physiological community worldwide. It is in this context that the Committee has played a major role by contributing to the IUPS Congresses. Since 2001 there have been four Congresses, including the Congress to be held in Rio de Janeiro. Each Congress has provided an amazing opportunity to connect with students, post-docs and junior and senior physiologists.

In San Diego, USA, 2005 the Congress title was "From Genomes to Functions" and fitting with the theme of the Congress the Walter C. Randall lecture given by Professor Robert Williamson was titled "The Future of Physiology in the Era of the Human Genome: Medical Miracles or Ethical Dilemmas?" The lecture was immediately followed by a panel discussion with a number of notable ethicists and physiologists: E. R. Weibel, B. M. Knoppers, A. W. Cowley, D. A. Prentice and P. Corvol

In Kyoto Japan 2009, "Functions of Life: Elements of Integration" was the theme of the Congress and the Ethics Committee sponsored an ethics symposium on "Best Practices in Physiological Research: Ethics and Integrity. The symposium focused on talks highlighting both the importance of animal research, the attention to the humane and ethical treatment of animals in physiological research and the importance of integrity in physiology research and the consequences of research misconduct. The speakers included C. Blakemore, N. Kagiyama, K. Barrett and P. Moody-Corbett.

In 2013, the 37th Congress was co-hosted with The Physiological Society meeting in Birmingham UK. The Ethics Committee sponsored a symposium highlighting a topic of community concern "Synthetic Biology: Scientific progress or ethical dilemma". The

presenters provided both physiological and ethical perspectives on this topic and included: F. Kepes, T. Baldwin, D. Milius, C. Rhodes and D. Benoit-Browaeyes.

In 2017 we are celebrating the "Rhythms of Life" at the 38th IUPS Congress and for this Congress the Ethics Committee is pleased to sponsor a symposium which will highlight the members of the Ethics Committee: "Promoting Ethical Practices in Physiological Research". The focus of the presentations will be on "Knowing what is right and Doing what is right". The scientific rationale for this symposium is to promote ethical research practices, from planning to publishing, for all of our research community, particularly early career scientists, to support the best physiological research possible. In addition to three members of the Ethics Committee, P. Moody-Corbett, A. Anand and B. Yates, we are happy to be joined by S. Vasconcelos, an early career researcher from Brazil.

The IUPS Congresses continue to be the best opportunity for dissemination of the topics of research ethics and integrity to a wide selection of international physiologists at all career levels.

Ethical issues in Experimental Animal Physiology

Experiment (in Latin *experiri* – to try, to attempt) signifies the repeated observation under simplified and standardized conditions. An *in vivo* experiment is an important part of Physiology. It indicates an experiment with/on living organism and requires utilization of laboratory animals. Over the years, the use of animals in research has become morally justifiable in the light of the potential health "benefits" in relation to the experiments. Most often mice, rats, rabbits and guinea pigs are used. Especially mice and rats are highly popular among researchers as they are small and have short reproduction cycles. The special kinds of

experiments are those in activity Physiology (“Actophysiology”), which are in many aspects more complicated than research on restrained and anesthetized animal. Because these experiments are usually long-term, the adaptation of animals is necessary. Moreover, surgical interventions are very specific in order to make both registration and application of stimuli possible. However, research in the field of activity Physiology affords results that are specific and representative for living organisms during locomotion and exercise (15).

Legislation and ethics in animal research is one of the main parts of laboratory animal science. As long as animals have been used in experiments there has been a deep concern about it. This has led to development of guidelines and restrictions of different kinds. The first law to be adopted was the “Cruelty to Animals Act” in Great Britain in 1876. This Act did require the use of anaesthetics for many types of animal experimentation and it was in force for more than 100 years.

Council for International Organizations of Medical Sciences (CIOMS) and International Council for Laboratory Animal Science (ICLAS) prepared revised International Guiding Principles for Biomedical Research Involving Animals (20). This document reflects current best practices and standards of care in laboratory animal medicine and science and provides the framework of responsibility and oversight to ensure the appropriate use of animals. This document has been the framework for the development of laws, policies, and guidelines for over 30 years. When Guiding Principles were written in 1985, the profession of laboratory animal medicine and science was still establishing best practices and standards of care. Since the publication of the original Guiding Principles, the scope of animal research has expanded significantly, numerous technological advancements have occurred, and societal attention to the welfare of research animals has increased. This evolution has prompted an update and

expansion of the focus of the Guiding Principles is to address contemporary issues facing scientists when animals are used for research and education.

The International Guiding Principles for Biomedical Research Involving Animals were adopted by international organizations and governmental agencies and are used by scientific community worldwide. Today most developed countries have adopted their own laws for animal protection. However, laws and decrees are always too remote to give full protection to the animals (12). At the end it is the attitude of the people that handle the animals that is the most important thing. Promotion and development of such attitudes is one of laboratory animal science most important duties. In many countries, Ethical committees have been set up to stimulate ethical discussions and improve ethical consciousness.

Future challenges

Still there is the discussion regarding the use of animals in medical research. Among all topics, several subjects seem to be of special interest (30). First, although detailed regulations governing the use of animals in research have been in place for several decades, there is a problem with upholding these regulations. The question also is if scientists pay enough attention to the justification of the increasing numbers of experimental animals required to conduct biomedical studies. Second, the formation of radical animal-rights organizations that do not see the potential health benefits and consider all animal research unethical. Finally, it is important to mention that several decades' worth of experience with current regulations regarding the use of animals in biomedical research has produced a strong moral consensus for these practices. Probably the importance of increased regulatory vigilance should be pointed out.

Authorship issues

Most scientific research these days is a collaborative activity. It is being carried out not only interdepartmentally but also inter-institutionally and increasingly across the globe. The requirement of funding agencies that support most research work is to have the outcomes communicated and this is done by writing of scientific papers. Thus beyond conducting ethically approved research projects and obtaining informed consent wherever required, there exist important issues of communicating the scientific outcome with fairness and integrity. Of these, 'appropriate authorship' is one of the most important ones. Being an 'author' accrues great benefit to the researcher as it provides academic and professional standing, credibility in the chosen field and a means for career enhancement. Some of the benefits that a long list of published work can provide include enabling authors to apply to or be nominated for academic awards and eventually to academic-empire building. An example of the latter is to get recognition for what they project as their exclusive contribution in their field so as to have new research centers or even institutes setup around these.

Inappropriate Authorship

However complaints of younger researchers who have contributed substantially to a study, of having being denied first authorship or authorship at all are being seen increasingly. Instances of insertion of names of non-participants in the study, but who were either involved in acquiring funds for it or of a head or a senior member of their laboratory or head of the Institution, are becoming ever more obvious. This situation is further complicated by the fact that some organizations have also started to include the names of 'ghost writers' i.e., those who have only written up but not participated in the study.

The way forward

All persons designated as authors should have made substantial contributions to the conception and design of the study, its supervision and or acquisition of data, its analysis, interpretation and writing of substantial parts of the paper. But as far as listing of authors is concerned generally (this is not the case in all disciplines) the first author by definition or practice is one who has done most of the experimental work and writes substantial parts or all of the paper and thus is *able to reply to reviewers' queries and stand up to their criticism.*

Given the above criteria one can then differentiate between those who have contributed to the conduct of the study, yet cannot be considered as qualifying as authors. These would be individuals who have provided technical assistance, who have run the necessary equipment, provided the manual labor of data gathering for large studies, assisted with patients if they were part of the study or carried out the statistical analyses. In addition they would be those who were involved in acquiring funding for the project or the study or editing the manuscript after it has been written up. This category of contributors does not have the intellectual ownership or responsibility for the final product or findings. However they would be made preeminent in the list of contributors to be acknowledged at the end of the publication.

Finally it is to be emphasized that with having claimed credit and acknowledged responsibility of their findings the task of the authors is not over. The new scientific knowledge that has been created and put into print has now to be disseminated by presenting it at scientific meeting, symposia and congresses. Appropriate authorship requires that each of those who have been listed as authors and irrespective of whether their contribution amounted to 10%, 20%, or more should be able to present it to an audience, to answer questions and be able to provide future directions of the work in order to qualify as authors of

that piece of work. Otherwise they should only be acknowledged for whatever they have contributed to the study. (source reference, 2)

Reproducibility and Reliability of Research

The reproducibility and reliability of biomedical research is firmly in the spotlight these days. The Oxford English Dictionary defines (scientific) reproducibility as *the extent to which consistent results are obtained when an experiment is repeated.* Reproducibility is a fundamental principle of scientific research and published science is expected to be reproducible.

However, reproducibility has come under intense scrutiny in recent years. A recent UK symposium co-hosted by the Academy of Medical Sciences, the Biotechnology & Biological Sciences Research Council, the Medical Research Council and Wellcome generated a formal call to action to improve reproducibility and reliability of biomedical research in the UK from the host organizations (27). In late 2016, the InterAcademy Partnership for Health published a similarly-intentioned statement, endorsed by 46 national Academies (1). The Reproducibility Project aims to repeat 100 published experimental and correlational psychological studies: the work is being led by the Centre for Open Science (8), whose goal is to increase the openness, integrity and reproducibility of scientific research. Nature published a special edition recently – *Challenges in Reproducible Research* – to promote awareness of the issue within the scientific community and to promote their mission to improve the transparency and robustness of what they publish (24). The list could continue.

The reasons for (ir)reproducible science are varied. It may be poorly conducted science. A recent survey of researchers found that 87% of more than 1,576 researchers (which included

over 700 biologists) named poor experimental design as a cause of irreproducibility, and 89% named flaws in statistical analysis (5). The exact magnitude of the issue can be difficult to establish, given studies may not be replicated exactly, and statistically one expects failure in replication. The oft-cited publication bias to publish positive results can generate compounding challenges to reproducibility: the implication that researchers seek to find positive – and therefore publishable – results, and the career and reputation disincentives that travel with a lesser publication track record.

There are many reasons to argue for the principle and practice of reproducibility, and important amongst those is the imperative for excellent research training of Masters and PhD candidates. These are, after all, the people who will continue the scientific endeavor on our behalf.

A powerful anecdote is provided by Alyssa Ward, reported in Nature (4). In the course of her PhD, Alyssa was citing a meta-analysis of studies on reproducibility, which identified that scientists routinely fail to explain how they choose the number of samples to use in their studies. What startled Alyssa was her realization that she had no idea 'how, or when, to calculate sample size'. She knew not to forge data. But what she *needed* to know was how to achieve valid findings through excellent research design. 'Mistakes are more important than misconduct', she is quoted as saying in the article. 'I wanted a course on mistakes.'

Reassuringly, and although the literature is arguably focused on the factors that contribute to the irreproducibility of scientific findings, there are significant practical steps being taken to foreground this issue and to optimize the validity of research findings.

A good example is the UK symposium referred to previously (27). The symposium sponsors – who include major funders of research – have since collaborated on a range of measures focused on improving: the openness and transparency of methods, data and results; research design and the completeness of reporting; funding decisions; and education & training. Some of these measures are mirrored in initiatives elsewhere, and it is clear that there is a concerted effort being staged world-wide to ensure that research is as valid, efficient and productive as possible.

Publication Ethics and Impacts on Physiology

A variety of problems in the publication of physiological data have recently been described, which diminish the quality of the scientific literature, and may eventually erode public confidence in the scientific enterprise. These problems include:

- Inadequate description of the methodology used in experiments, and "cherry-picking" of data, such that findings cannot be reproduced between laboratories (11, 22, 23, 31, 33).
- Faulty statistical analysis of data, resulting in reporting of false positive or negative results (9, 10, 25).
- Unreliability of the peer review process, allowing flawed manuscripts to be published and meritorious manuscripts to be rejected (34).

These problems will be discussed below, along with efforts of scientific publishers to address the concerns.

A number of recent articles (11, 22, 23, 31, 33) including those in the popular press (19, 32) have discussed an increasing unreliability of published scientific findings. A number of factors have been attributed as contributing to the diminished quality of published scientific

data, particularly the competitiveness of the academic environment (29). Scientists often rush to get their data into print, without adequate replication of the findings. They also may not have sufficient resources to repeat experiments that were potentially contaminated. In addition, scientists may not be aware of the effects on experimental results of extraneous factors such as the bedding and diet of research animals. Moreover, it has become uncommon to publish negative data or to replicate studies conducted in other labs, so investigators are unsure whether their conclusions are valid.

Another issue of concern is the use of inappropriate statistical methods when analyzing data (9, 10, 25). Such flawed data analysis can result from an inadequate background in statistics, or intentional use of inappropriate practices such as p-hacking (repeating an experiment only until statistically significant findings are obtained). Conducting a study with too few research subjects (or too few samples), or use of a statistical method that is not sufficiently rigorous, can result in flawed conclusions.

As discussed in a recent editorial (34), it is also becoming increasingly difficult to secure qualified reviewers to provide editorial feedback on papers. As a result, peer review is often left to less qualified experts, who can provide misleading advice to editors, who in turn make a poor editorial decision. One trend is for senior investigators to defer peer review to their trainees (29). Although it is highly encouraged for investigators to involve their students and postdoctoral associates in peer review to provide critical training, the exercise is only effective if mentors offer oversight for the process. Unless senior investigators consider peer review to be a critical component of their professional lives, the primary gatekeeper for the scientific literature will be lost.

Even more troubling is the emergence of new "predatory" scientific journals that claim to conduct peer review, but really don't (6, 7, 13, 17). It is possible to publish a paper in such a journal that has not been rigorously scrutinized. If a study is funded by government agencies like the National Institutes of Health (NIH), then a related publication in a predatory journal will be indexed in search engines such as PubMed, leading many readers to falsely believe that it has been subjected to a thorough editorial process (16).

In response to these troubling developments, a number of publishers have taken some steps to improve the quality of the manuscripts that they publish. They include checklists for authors and reviewers to assure that all salient methodological details are included in articles (3, 18), and the addition of a statistical reviewer for submissions (9, 25, 28). Some journals are also requiring the inclusion of a power analysis in manuscripts to demonstrate that the sample size for the study was adequate (31). New legitimate open-access journals have emerged to provide outlets for publication of negative data (26). Organizations like scholarly open access are providing information to authors about predatory journals (6), and there are actions in courts to suppress predatory publishers (14). Journals are increasingly offering venues for authors to provide feedback about the articles they read (21).

However, scientists and scientific administrators must do a better job of self- policing to assure the validity of the scientific literature. Pressure to publish in high impact factor journals must subside; investigators should be rewarded for the quality of the work that they publish, and not the name of the journal it is published in. Granting agencies should appreciate the importance of replicating data, and provide funding to do so. Senior scientists must understand that performing thorough and timely peer review of articles is their responsibility, and their supervisors must value these peer review activities. Failure to take

these steps will result in wasted scientific efforts, diminished confidence of the public in the research enterprise, and ultimately the loss of monetary investment in research.

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The Future of Computational Physiology and Medicine

Andrew D. McCulloch*

Departments of Bioengineering and Medicine

University of California San Diego

9500 Gilman Drive

La Jolla, CA

92093-0412, USA

* Chair of the International Union of Physiological Sciences, Physiome and Systems Biology Committee

Address for Correspondence:

Dr. Andrew D. McCulloch

Departments of Bioengineering and Medicine

University of California San Diego

9500 Gilman Drive

La Jolla, CA

92093-0412, USA

Email: amcculloch@eng.ucsd.edu

Running Head: The Physiome

Abstract

The IUPS has been at the forefront of promoting collaborative international research on multi-scale computational modeling and systems biology physiology. Recent progress in this field is paving the way for fundamental advances in computer-aided physiology and personalized medicine.

Key words:

Physiome, Systems Biology, Multi-Scale Modeling

The sequencing of the human genome and the advent of the big data era of biomedical science have driven the vision of a new personalized medicine enabled by the new universe of personal health data that technologies like DNA sequencing, transcriptomics, proteomics, metabolomics and microbiome profiling promise to deliver to physicians. But standing in the way of this new era of medicine are the weak correlations found in most GWAS studies and the realization that personalized diagnosis can only be translated to personalized therapy with a much larger pharmacy of individualized combination therapies. Hence, the more immediate, if less ambitious, goal has turned to "precision medicine", which aims to refine the taxonomy of disease to better reflect the specific molecular etiology and thus inform the optimal choice of targeted therapeutics. Already this approach is allowing clinical trials of new cancer therapeutics to be tested in better selected patient cohorts and is leading to promising outcomes. But how readily this strategy will translate to many other diseases will depend on how well biomedical science can reliably integrate from genome to physiome so that the natural history of disease and responses to therapy can be predicted in individual patients. Fortunately, the international physiology community in general - and the IUPS in particular - has been at the forefront of mapping the path to this goal for the past quarter of a century.

Predictive, mechanistic mathematical models have informed experiments and enhanced understanding of physiology since Poiseuille and Hagen, Krogh and Huxley. In the 21st century, building on the success of reductionist biological science, modern computational physiology has provided powerful tools to integrate this new information into physiological knowledge. Indeed, computational approaches facilitate the goal of integration in three separate yet highly complementary ways: *Information* or *data integration* is the goal of bioinformatics, which annotates, archives, searches, compares and mines the troves of

genome-scale biological data; With the list of components in hand, it becomes possible to reconstruct and model the cellular networks involved in signaling and gene expression, protein synthesis and degradation, metabolism and other cell functions. This *functional integration* is the goal of systems biology, which attempts to build computational models that predict the emergent functions of these cellular networks from the functional interactions of their components. But neither a complete parts list nor large, comprehensive network models of cellular subsystems and their dynamics are sufficient alone to explain normal organ, system and whole body physiology, much less the phenotypes of disease and aging. This missing link, of course, is *structure*. The third way in which computation can be integrative is structurally across physical scales of biological organization from molecular to population scales. In contrast to data-driven systems biology, multi-scale biological modeling is physics-driven and limited in large part by available computational power. But rapid advances in algorithms and computer hardware performance are beginning to push atomic-resolution molecular models to physiologically relevant spatial and temporal scales, and also advancing multi-scale cell-to-organ models towards clinical feasibility.

Integrated multi-scale models of physiological structure-function relations and pathophysiological dysfunction actually require the synthesis of all three computational approaches to integration: bioinformatics to organize molecular, structural and functional data; molecular modeling to predict the proximal effects of drugs, mutations, polymorphisms, or post-translational modifications; systems biology to integrate those molecular functions into network models of cellular dynamics, and anatomically explicit multi-scale "physiome" models of cell to organism scale biophysics and physiology. This ambitious vision of a new computational physiology was first articulated nearly three decades ago by Denis Noble at Oxford and James Bassingthwaighte in Seattle. They gave us the Physiome moniker and,

along with Peter Hunter (New Zealand), Aleksander Popel (USA), Yung Earm (South Korea), Akinori Noma (Japan), Adriano Henney (UK) and many others established the IUPS as it's leading international flag-bearer.

I have not yet seen a fully executed example of a multi-scale physiome model that has integrated from atomic molecular dynamics to whole body systems physiology, but in some areas such as cardiac, liver and microvascular physiology just about every bridge between scales has been built, and in some cases many of the scales of biological organization have already been spanned - from atoms to molecules, molecules to complexes, complexes to networks, networks to cells, single cells to multi-cellular tissue niches, tissues to organ, organs to system, systems to whole organism, and organisms to populations. I would not be surprised to see the first complete example by the time of the 2021 congress. Needless to say, the approach is not to model every atom in the body. The challenge is in identifying, for the problem at hand, the variables that must be exchanged between one scale and the next, and the answer will invariably depend on the problem that the model is addressing. In some cases, cellular noise and stochasticity, or multi-cellular heterogeneity are critical to understanding emergent tissue functions, while in others mean field approximations can be sufficient. In some problems the paracrine interactions between different cell types are paramount, whereas in others a single cell type may be sufficient to predict the organ-scale phenotype.

As new paradigms for genome to physiome modeling are developed, shared and validated with properly designed physiological experiments, the way that physiologists design and conduct experiments will change. Increasingly, we will turn first to computational models to generate and test hypotheses *in silico*, to understand sources of variability better, to identify physiological responses that are most sensitive to upstream perturbations, and to better

understand homeostasis and physiological robustness and how they are changed by aging and disease. Failure of model prediction will become as valuable as success, by pointing to areas where new mechanisms are needed and in turn leading to better models.

While multi-scale physiome modeling is already experiencing success in bridging wide ranges of spatial scale, the ranges of *temporal* scale in physiology are even greater, from the picosecond scale of atomic motions to the decades of human life-span and the generations of evolutionary time. Among the most pressing immediate challenges in modern multi-scale modeling is extending models of cell, tissue and organ physiology to the time-scales of development, the natural history of disease and aging. But as models of gene regulatory networks, transcription and translation in mammalian cells continue to improve, it is now realistic to anticipate a new generation of physiome model that remodel themselves over periods of days, weeks, months and perhaps even longer. Today's engineers use computational simulations for "accelerated wear testing" of their designs so that lifetime performance can be predicted in a fraction of real time. We are starting to see the first examples of this new class of model in simulations of chronic pathophysiological processes and therapeutic responses.

So how does all of this progress advance the vision of personalized, precision computational medicine? Already in musculoskeletal, cardiac, lung, blood, liver, metabolic and infectious diseases, modeling is being tested to plan surgical procedures, provide clinical decision support for device therapies and medical management of individual patients, to optimize pharmacotherapies, design better clinical trials, provide training simulators, and predict the spread of infectious outbreaks. As these clinical and patient-specific models become less empirical and more mechanistic by spanning more scales of biological organization, they will

become a natural foundation for fusing biomedical “big data” in a rationale, disease-centric and patient-specific way. The notion that machine learning will improve health by mining everything from our genomes to our Facebook profiles is largely a fantasy to most physiologists who know that the foundations of medical science are much more than a large stack of data but the culmination of centuries of carefully designed models and experiments, hypothesis testing, quantitative analysis and theoretical analysis. Only with carefully validated, mechanistic functionally and structurally integrated multi-scale models can the opportunities for biomedical big data fusion and computational medicine be realized. Fortunately, the IUPS is leading the way.

The Physiological Society